10/799,676

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=> d his

     (FILE 'HOME' ENTERED AT 08:53:58 ON 03 JUN 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 08:54:24 ON 03 JUN 2005
L1       1322846 S KINASE?
L2           551 S SR (5W)L1
L3           166 S HUMAN AND L2
L4            62 DUP REM L3 (104 DUPLICATES REMOVED)
L5           109 S "SRPK"
L6       7101940 S CLON? OR EXPRESS? OR RECOMBINANT
L7            54 S L5 AND L6
L8            19 DUP REM L7 (35 DUPLICATES REMOVED)
                 E ABU-THREIDEH J/AU
                 E ABU  J T/AU
                 E GONG F/AU
L9           238 S E3
                 E KETCHUM K A/AU
L10          480 S E3-E7
                 E DIFRANCESCO V/AU
L11          100 S E3
                 E BEASLEY E M/AU
L12          327 S E3
L13          993 S L8 OR L9 OR L10 OR L11 OR L12
L14          227 S L3 OR L5
L15           21 S L13 AND L14
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NEWS	2		"Ask CAS" for self-help around the clock
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NEWS	4	FEB 28	PATDPAFULL - New display fields provide for legal status data from INPADOC
NEWS	5	FEB 28	BABS - Current-awareness alerts (SDIs) available
NEWS	6	FEB 28	MEDLINE/LMEDLINE reloaded
NEWS	7	MAR 02	GBFULL: New full-text patent database on STN
NEWS	8	MAR 03	REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS	9	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS	10	MAR 22	KOREAPAT now updated monthly; patent information enhanced
NEWS	11	MAR 22	Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS	12	MAR 22	PATDPASPC - New patent database available
NEWS	13	MAR 22	REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS	14	APR 04	EPFULL enhanced with additional patent information and new fields
NEWS	15	APR 04	EMBASE - Database reloaded and enhanced
NEWS	16	APR 18	New CAS Information Use Policies available online
NEWS	17	APR 25	Patent searching, including current-awareness alerts (SDIs), based on application date in CA/CAplus and USPATFULL/USPAT2 may be affected by a change in filing date for U.S. applications.
NEWS	18	APR 28	Improved searching of U.S. Patent Classifications for U.S. patent records in CA/CAplus
NEWS	19	MAY 23	GBFULL enhanced with patent drawing images
NEWS	20	MAY 23	REGISTRY has been enhanced with source information from CHEMCATS
NEWS	21	MAY 26	STN User Update to be held June 6 and June 7 at the SLA 2005 Annual Conference

NEWS EXPRESS JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005

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=> file medline embase biosis biotechds scisearch hcaplus ntis lifesci
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FILE 'LIFESCI' ENTERED AT 08:54:24 ON 03 JUN 2005
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=> s kinase?
L1     1322846 KINASE?

=> s SR (5w)l1
L2          551 SR (5W) L1

=> s human and l2
L3          166 HUMAN AND L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4            62 DUP REM L3 (104 DUPLICATES REMOVED)

=> d 1-62 ibib ab

L4   ANSWER 1 OF 62  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:121193  HCAPLUS
DOCUMENT NUMBER:          142:214836
TITLE:                    Biomarkers of cyclin-dependent kinase modulation in
                          cancer therapy
INVENTOR(S):              Li, Martha; Rupnow, Brent A.; Webster, Kevin R.;
                          Jackson, Donald G.; Wong, Tai W.
PATENT ASSIGNEE(S):       Bristol-Myers Squibb Company, USA
```

SOURCE: PCT Int. Appl., 141 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005012875	A2	20050210	WO 2004-US24424	20040729

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-490890P P 20030729

AB Biomarkers having expression patterns that correlate with a response of cells to treatment with one or more cdk modulating agents, and uses thereof. Transcription profiling was used to identify the biomarkers. Specifically, transcription profiling of the effect of a certain cdk2 inhibitor (BMS 387032 0.5 L-tartaric acid salt) on peripheral blood mononuclear cells was first performed. Gene chips were used to quantitate the levels of gene expression on a large-scale with Affymetrix **human** gene chips HG-U95A, B, and C. Next, profiling of a cdk2 inhibitor-treated tumor cell line A28780 at multiple doses and time points was performed to establish a correlation of tumor site response with peripheral blood biomarkers. In order to establish the mol. target-specificity of the potential biomarkers, tumor cell line A2780 treated with anti-cdk2 oligonucleotides was also profiles. Overlapping gene expression changes were selected for further evaluation in **human** ovarian carcinoma xenograft A2780 that were treated with the cdk2 inhibitor. The selected biomarkers were subjected to real-time PCR anal. in order to verify the observed changes from the gene chip anal. The biomarker comprising GenBank accession number W28729 was discovered to have the most consistent and robust regulation in response to cdk inhibition. Provided are methods for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer that comprises administering an agent that modulates cdk activity.

L4 ANSWER 2 OF 62 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:1099 SCISEARCH
THE GENUINE ARTICLE: 878AL
TITLE: LTD4 induces hyperresponsiveness to histamine in bovine airway smooth muscle: role of **SR**-ATPase Ca2+ pump and tyrosine **kinase**
AUTHOR: Carbajal V; Vargas M H; Flores-Soto E; Martinez-Cordero E; Bazan-Perkins B; Montano L M (Reprint)
CORPORATE SOURCE: Inst Nacl Enfermedades Resp, Lab Invest Autoinmunidad, Tlalpan 4502, Mexico City 14080, DF, Mexico (Reprint); Inst Nacl Enfermedades Resp, Lab Invest Autoinmunidad, Mexico City 14080, DF, Mexico; Inst Nacl Enfermedades Resp, Dept Hiperreactividad Bronquial, Mexico City 14080, DF, Mexico; Univ Nacl Autonoma Mexico, Fac Med, Dept Farmacol, Mexico City 04510, DF, Mexico
COUNTRY OF AUTHOR: Mexico
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-LUNG CELLULAR AND MOLECULAR

PHYSIOLOGY, (JAN 2005) Vol. 288, No. 1, pp. L84-L92.
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 1040-0605.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Airway hyperresponsiveness is a key feature of asthma, but its mechanisms remain poorly understood. Leukotriene D-4 (LTD4) is one of the few molecules capable of producing airway hyperresponsiveness. In this study, LTD4, but not leukotriene C-4 (LTC4), produced a leftward displacement of the concentration-response curve to histamine in bovine airway smooth muscle strips. Neither LTC4 nor LTD4 modified the concentration-response curve to carbachol. In simultaneous measurements of intracellular Ca2+ ([Ca2+](i)) and contraction, histamine or carbachol produced a transient Ca2+ peak followed by a plateau, along with a contraction. LTD4 increased the histamine-induced transient Ca2+ peak and contraction but did not modify responses to carbachol. Enhanced responses to histamine induced by LTD4 were not modified by staurosporine or chelerythrine but were abolished by genistein. Western blot showed that carbachol, but not histamine, caused intense phosphorylation of extracellular signal-regulated kinase 1/2 and that LTD4 significantly enhanced the phosphorylation induced by histamine, but not by carbachol. L-type Ca2+ channel participation in the hyperresponsiveness to histamine was discarded because LTD4 did not modify the [Ca2+](i) changes induced by KCl. In tracheal myocytes, LTD4 enhanced the transient Ca2+ peak induced by histamine (but not by carbachol) and the sarcoplasmic reticulum (SR) Ca2+ refilling. Genistein abolished this last LTD4 effect. Partial blockade of the SR-ATPase Ca2+ pump with cyclopiazonic acid reduced the Ca2+ transient peak induced by histamine but not by carbachol. These results suggested that LTD4 induces hyperresponsiveness to histamine through activation of the tyrosine kinase pathway and an increasing SR-ATPase Ca2+ pump activity. L-type Ca2+ channels seemed not to be involved in this phenomenon.

L4 ANSWER 3 OF 62 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:413282 SCISEARCH
THE GENUINE ARTICLE: 916SR
TITLE: Intracellular calcium release and cardiac disease
AUTHOR: Wehrens X H T (Reprint); Lehnart S E; Marks A R
CORPORATE SOURCE: Columbia Univ Coll Phys & Surg, Dept Med, Ctr Mol Cardiol, Dept Physiol & Cellular Biophys, 630 W 168th St, New York, NY 10032 USA (Reprint); Columbia Univ Coll Phys & Surg, Dept Med, Ctr Mol Cardiol, Dept Physiol & Cellular Biophys, New York, NY 10032 USA
COUNTRY OF AUTHOR: USA
SOURCE: ANNUAL REVIEW OF PHYSIOLOGY, (MAY 2005) Vol. 67, pp. 69-98

Publisher: ANNUAL REVIEWS, 4139 EL CAMINO WAY, PO BOX 10139, PALO ALTO, CA 94303-0139 USA.
ISSN: 0066-4278.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 221

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Intracellular calcium release channels are present on sarcoplasmic and endoplasmic reticuli (SR, ER) of all cell types. There are two classes of these channels: ryanodine receptors (RyR) and inositol 1,4,5-trisphosphate receptors (IP3R). RyRs are required for excitation-contraction (EC) coupling in striated (cardiac and skeletal) muscles. RyRs are made up of macromolecular signaling complexes that contain large cytoplasmic domains,

which serve as scaffolds for proteins that regulate the function of the channel. These regulatory proteins include calstabin1/calstabin2 (FKBP12/FKBP12.6), a 12/12.6 kDa subunit that stabilizes the closed state of the channel and prevents aberrant calcium leak from the **SR**. **Kinases** and phosphatases are targeted to RyR2 channels and modulate RyR2 function in response to extracellular signals. In the classic fight or flight stress response, phosphorylation of RyR channels by protein kinase A reduces the affinity for calstabin and activates the channels leading to increased SR calcium release. In heart failure, a cardiac insult causes a mismatch between blood supply and metabolic demands of organs. The chronically activated fight or flight response leads to leaky channels, altered calcium signaling, and contractile dysfunction and cardiac arrhythmias.

L4 ANSWER 4 OF 62 MEDLINE on STN
ACCESSION NUMBER: 2004141137 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14718546
TITLE: Regulation of binding of lamin B receptor to chromatin by **SR** protein **kinase** and cdc2 **kinase** in Xenopus egg extracts.
AUTHOR: Takano Makoto; Koyama Yuhei; Ito Hiromi; Hoshino Satomi; Onogi Hiroshi; Hagiwara Masatoshi; Furukawa Kazuhiro; Horigome Tsuneyoshi
CORPORATE SOURCE: Course of Biosphere Science, Graduate School of Science and Technology, Faculty of Science, Niigata University, Igarashi-2, Niigata 950-2181, Japan.
SOURCE: Journal of biological chemistry, (2004 Mar 26) 279 (13) 13265-71. Electronic Publication: 2004-01-12. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20040323
Last Updated on STN: 20040510
Entered Medline: 20040507

AB Participation of multiple kinases in regulation of the binding of lamin B receptor (LBR) to chromatin was suggested previously (Takano, M., Takeuchi, M., Ito, H., Furukawa, K., Sugimoto, K., Omata, S., and Horigome, T. (2002) Eur. J. Biochem. 269, 943-953). To identify these kinases, regulation of the binding of the nucleoplasmic region (NK, amino acid residues 1-211) of LBR to sperm chromatin was studied using a cell cycle-dependent Xenopus egg extract in vitro. The binding was stimulated on specific phosphorylation of the NK fragment by an S-phase egg extract. Protein depletion with beads bearing SF2/ASF, which binds **SR** protein **kinases**, abolished this stimulation, suggesting that an **SR** protein **kinase**(s) is responsible for the activation of LBR. This was confirmed by direct phosphorylation and activation with recombinant **SR** protein-specific **kinase** 1. The binding of the NK fragment to chromatin pretreated with an S-phase extract was suppressed by incubation with an M-phase extract. Enzyme inhibitor experiments revealed that multiple kinases participate in the suppression. One of these kinases was shown to be cdc2 kinase using a specific inhibitor, roscovitine, and protein depletion with beads bearing p13, which specifically binds cdc2 kinase. Experiments involving a mutant NK fragment showed that the phosphorylation of serine 71 by cdc2 kinase is responsible for the suppression.

L4 ANSWER 5 OF 62 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004128571 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14701833
TITLE: Temporal association of protamine 1 with the inner nuclear

membrane protein lamin B receptor during spermiogenesis.
AUTHOR: Mylonis Ilias; Drosou Victoria; Brancorsini Stefano; Nikolakaki Eleni; Sassone-Corsi Paolo; Giannakouros Thomas
CORPORATE SOURCE: Laboratory of Biochemistry, Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54 124, Greece.
SOURCE: Journal of biological chemistry, (2004 Mar 19) 279 (12) 11626-31. Electronic Publication: 2003-12-30. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20040316
Last Updated on STN: 20040528
Entered Medline: 20040527

AB During mammalian spermiogenesis, histones are replaced by transition proteins, which are in turn replaced by protamines P1 and P2. P1 protamine contains a short arginine/serine-rich (RS) domain that is highly phosphorylated before being deposited into sperm chromatin and almost completely dephosphorylated during sperm maturation. We now demonstrate that, in elongating spermatids, this phosphorylation is required for the temporal association of P1 protamine with lamin B receptor (LBR), an inner nuclear membrane protein that also possesses a stretch of RS dipeptides at its nucleoplasmic NH(2)-terminal domain. Previous studies have shown that the cellular protein p32 also binds tightly to the unmodified RS domain of LBR. Extending those findings, we now present evidence that p32 prevents phosphorylation of LBR and furthermore that dissociation of this protein precedes P1 protamine association. Our data suggest that docking of protamine 1 to the nuclear envelope is an important intermediate step in spermiogenesis and reveal a novel role for **SR** protein **kinases** and p32.

L4 ANSWER 6 OF 62 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 2
ACCESSION NUMBER: 2005:131099 BIOSIS
DOCUMENT NUMBER: PREV200500132041
TITLE: Hypoxic pulmonary vasoconstriction: redox regulation of O2-sensitive K+ channels by a mitochondrial O2-sensor in resistance artery smooth muscle cells.
AUTHOR(S): Michelakis, Evangelos D.; Thebaud, Bernard; Weir, E. Kenneth; Archer, Stephen L. [Reprint Author]
CORPORATE SOURCE: Dept MedDiv Cardiol, Univ Alberta, WMC 2C2-36,8440 112th St, Edmonton, AB, T6G 2B7, Canada
sarcher@cha.ab.ca
SOURCE: Journal of Molecular and Cellular Cardiology, (December 2004) Vol. 37, No. 6, pp. 1119-1136. print. ISSN: 0022-2828 (ISSN print).
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Apr 2005
Last Updated on STN: 6 Apr 2005

AB Hypoxic pulmonary vasoconstriction (HPV) is a widely-conserved mechanism for matching ventilation and perfusion that optimzes systemic PO2. HPV is elicited by moderate alveolar hypoxia through a mechanism that is intrinsic to the Pulmonary circulation, particularly the resistance pulmonary arteries (PA), and is robust even in isolated perfused lungs. Although modulated by the enclotheliLlIll, HPV persists in denuded PA rings and PA smooth muscle cells (PASMC). Beginning within seconds of hypoxia, HPV plateaus in minutes and persists for hours. During focal hypoxia (e.g. atelectasis), HPV is restricted to the vascular segments

serving hypoxic lobes, and diverts blood to better-ventilated segments without causing Pulmonary hypertension (PHT). However, with global hypoxia, as occurs at high altitude or in the fetal lung, HPV increases pulmonary vascular resistance (PVR) and may contribute to PHT. This review focuses on a comprehensive Redox Theory of HPV but considers relevant modulatory factors (endothelin), triggering stimuli (cyclic ADP-ribose-induced release of sarcoplasmic reticulum (**SR**) Ca2+) and sustaining pathways (Rho **kinase**-modulated Ca2+ sensitization of the contractile apparatus). The Redox Theory proposes that all O2-sensor in resistance PASMC (complexes I and III of the mitochondrial electron transport chain (ETC)) generates reactive O2 species (ROS) in proportion to PO2. During normoxia, a redox mediator, like hydrogen peroxide (H2O2), maintains voltage-gated 0,sensitive K+ channels (Kv) in all oxidized open state. Hypoxic withdrawal of ROS inhibits Kv channels, thereby depolarizing PASMCs, activating L-type voltage-gated Ca2+ channels, enhancing Ca2+ influx and promoting vasoconstriction. The role of O2-sensitive K+ channels is conserved in most specialized O2-sensitive tissues, including the ductus arteriosus and carotid body. The unique occurrence of hypoxic vasoconstriction in the pulmonary circulation relates to the colocalization of an O2-sensor and O2-sensitive Kv channels in resistance PAs. HPV has relevance to **human** physiology, pathophysiology (high altitude pulmonary edema (HAPE) and PHT) and therapy (single lung anesthesia).

L4 ANSWER 7 OF 62 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2004510566 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15479736
TITLE: Hypophosphorylated SR splicing factors transiently localize around active nucleolar organizing regions in telophase daughter nuclei.
AUTHOR: Bubulya Paula A; Prasanth Kannanganattu V; Deerinck Thomas J; Gerlich Daniel; Beaudouin Joel; Ellisman Mark H; Ellenberg Jan; Spector David L
CORPORATE SOURCE: Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA.
CONTRACT NUMBER: GM 42694 (NIGMS)
SOURCE: Journal of cell biology, (2004 Oct 11) 167 (1) 51-63. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 20041014
Last Updated on STN: 20041219
Entered Medline: 20041122

AB Upon completion of mitosis, daughter nuclei assemble all of the organelles necessary for the implementation of nuclear functions. We found that upon entry into daughter nuclei, snRNPs and SR proteins do not immediately colocalize in nuclear speckles. SR proteins accumulated in patches around active nucleolar organizing regions (NORs) that we refer to as NOR-associated patches (NAPs), whereas snRNPs were enriched at other nuclear regions. NAPs formed transiently, persisting for 15-20 min before dissipating as nuclear speckles began to form in G1. In the absence of RNA polymerase II transcription, NAPs increased in size and persisted for at least 2 h, with delayed localization of SR proteins to nuclear speckles. In addition, SR proteins in NAPs are hypophosphorylated, and the **SR** protein **kinase** Clk/STY colocalizes with SR proteins in NAPs, suggesting that phosphorylation releases SR proteins from NAPs and their initial target is transcription sites. This work demonstrates a previously unrecognized role of NAPs in splicing factor trafficking and nuclear speckle biogenesis.

L4 ANSWER 8 OF 62 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2003507270 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14555757
TITLE: Processive phosphorylation of alternative splicing factor/splicing factor 2.
AUTHOR: Aubol Brandon E; Chakrabarti Sutapa; Ngo Jacky; Shaffer Jennifer; Nolen Brad; Fu Xiang-Dong; Ghosh Gourisankar; Adams Joseph A
CORPORATE SOURCE: Department of Pharmacology, University of California at San Diego, La Jolla, CA 92093-0506, USA.
CONTRACT NUMBER: GM 07752 (NIGMS)
GM 68168 (NIGMS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2003 Oct 28) 100 (22) 12601-6. Electronic Publication: 2003-10-10.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031030
Last Updated on STN: 20040106
Entered Medline: 20040105

AB SR proteins, named for their multiple arginine/serine (RS) dipeptide repeats, are critical components of the spliceosome, influencing both constitutive and alternative splicing of pre-mRNA. SR protein function is regulated through phosphorylation of their RS domains by multiple kinases, including a family of evolutionarily conserved **SR** protein-specific **kinases** (SRPKs). The SRPK family of kinases is unique in that they are capable of phosphorylating repetitive RS domains with remarkable specificity and efficiency. Here, we carried out kinetic experiments specially developed to investigate how SRPK1 phosphorylates the model **human** SR protein, ASF/SF2. By using the start-trap strategy, we monitored the progress curve for ASF/SF2 phosphorylation in the absence and presence of an inhibitor peptide directed at the active site of SRPK1. ASF/SF2 modification is not altered when the inhibitor peptide (trap) is added with ATP (start). However, when the trap is added first and allowed to incubate for a specific delay time, the decrease in phosphate content of the enzyme-substrate complex follows a simple exponential decline corresponding to the release rate of SRPK1. These data demonstrate that SRPK1 phosphorylates a specific region within the RS domain of ASF/SF2 by using a fully processive catalytic mechanism, in which the splicing factor remains "locked" onto SRPK1 during RS domain modification.

L4 ANSWER 9 OF 62 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003250087 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12773558
TITLE: Regulation and substrate specificity of the **SR** protein **kinase** Clk/Sty.
AUTHOR: Prasad Jayendra; Manley James L
CORPORATE SOURCE: Department of Biological Sciences, Columbia University, New York, New York 10027, USA.. jayendra10025@yahoo.com
SOURCE: Molecular and cellular biology, (2003 Jun) 23 (12) 4139-49.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030530

Last Updated on STN: 20030704
Entered Medline: 20030703

AB SR proteins constitute a family of splicing factors that play key roles in both constitutive and regulated splicing in metazoan organisms. The proteins are extensively phosphorylated, and kinases capable of phosphorylating them have been identified. However, little is known about how these kinases function, for example, whether they target specific **SR** proteins or whether the **kinases** themselves are regulated. Here we describe properties of one such kinase, Clk/Sty, the founding member of the Clk/Sty family of dual-specificity kinases. Clk/Sty is autophosphorylated on both Ser/Thr and Thr residues, and using both direct kinase assays and SR protein-dependent splicing assays, we have analyzed the effects of each type of modification. We find not only that the pattern of phosphorylation on a specific SR protein substrate, ASF/SF2, is modulated by autophosphorylation but also that the ability of Clk/Sty to recognize different SR proteins is influenced by the extent and nature of autophosphorylation. Strikingly, phosphorylation of ASF/SF2 is sensitive to changes in Tyr, but not Ser/Thr, autophosphorylation while that of SC35 displays the opposite pattern. In contrast, phosphorylation of a third SR protein, SRp40, is unaffected by autophosphorylation. We also present biochemical data indicating that as expected for a factor directly involved in splicing control (but in contrast to recent reports), Clk/Sty is found in the nucleus of several different cell types.

L4 ANSWER 10 OF 62 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003152252 EMBASE
TITLE: ICP27 interacts with SRPK1 to mediate HSV splicing inhibition by altering SR protein phosphorylation.
AUTHOR: Sciabica K.S.; Dai Q.J.; Sandri-Goldin R.M.
CORPORATE SOURCE: R.M. Sandri-Goldin, Department of Molecular Genetics, University of California, Irvine, CA 92697, United States. rmsandri@uci.edu
SOURCE: EMBO Journal, (1 Apr 2003) Vol. 22, No. 7, pp. 1608-1619.
Refs: 52
ISSN: 0261-4189 CODEN: EMJODG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030424
Last Updated on STN: 20030424

AB Infection with some viruses can alter cellular mRNA processing to favor viral gene expression. We present evidence that herpes simplex virus 1 (HSV-1) protein ICP27, which contributes to host shut-off by inhibiting pre-mRNA splicing, interacts with essential splicing factors termed SR proteins and affects their phosphorylation. During HSV-1 infection, phosphorylation of several SR proteins was reduced and this correlated with a subnuclear redistribution. Exogenous SR proteins restored splicing in ICP27-inhibited nuclear extracts and SR proteins isolated from HSV-1-infected cells activated splicing in uninfected S100 extracts, indicating that inhibition occurs by a reversible mechanism. Spliceosome assembly was blocked at the pre-spliceosomal complex A stage. Furthermore, we show that ICP27 interacts with SRPK1 and relocalizes it to the nucleus; moreover, SRPK1 activity was altered in the presence of ICP27 in vitro. We propose that ICP27 modifies SRPK1 activity resulting in hypophosphorylation of SR proteins impairing their ability to function in spliceosome assembly.

L4 ANSWER 11 OF 62 MEDLINE on STN DUPLICATE 6

ACCESSION NUMBER: 2003183383 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12549978

TITLE: Differential effects of hyperphosphorylation on splicing factor SRp55.
AUTHOR: Lai Ming-Chih; Lin Ru-Inn; Tarn Woan-Yuh
CORPORATE SOURCE: Graduate Institute of Life Sciences, National Defense Medical Center, Taipei, Taiwan, Republic of China.
SOURCE: Biochemical journal, (2003 May 1) 371 (Pt 3) 937-45. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030419
Last Updated on STN: 20030529
Entered Medline: 20030528

AB Members of the serine/arginine-rich (SR) protein family play an important role in both constitutive and regulated splicing of precursor mRNAs. Phosphorylation of the arginine/serine dipeptide-rich domain (RS domain) can modulate the activity and the subcellular localization of SR proteins. However, whether the SR protein family members are individually regulated and how this is achieved remain unclear. In this report we show that 5,6-dichloro-1 beta-D-ribofuranosyl-benzimidazole (DRB), an inhibitor of RNA polymerase II-dependent transcription, specifically induced hyperphosphorylation of SRp55 but not that of any other SR proteins tested. Hyperphosphorylation of SRp55 occurs at the RS domain and appears to require the RNA-binding activity. Upon DRB treatment, hyperphosphorylated SRp55 relocates to enlarged nuclear speckles. Intriguingly, SRp55 is specifically targeted for degradation by the proteasome upon overexpression of the **SR** protein **kinase** Clk/Sty. Although a destabilization signal is mapped within the C-terminal 43-amino acid segment of SRp55, its adjacent lysine/serine-rich RS domain is nevertheless critical for the Clk/Sty-mediated degradation. We report for the first time that SRp55 can be hyperphosphorylated under different circumstances whereby its fate is differentially influenced.

L4 ANSWER 12 OF 62 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2003055549 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12565829
TITLE: Protein kinase CK2 phosphorylates and activates the **SR** protein-specific **kinase** 1.
AUTHOR: Mylonis Ilias; Giannakouros Thomas
CORPORATE SOURCE: Laboratory of Biochemistry, Department of Chemistry, The Aristotelian University of Thessaloniki, Greece.
SOURCE: Biochemical and biophysical research communications, (2003 Feb 14) 301 (3) 650-6. Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030205
Last Updated on STN: 20030416
Entered Medline: 20030414

AB The serine/arginine subfamily of protein kinases has been conserved throughout evolution and its members are thought to play important roles in the regulation of multiple cellular processes. Mammalian SRPK1 has been considered as a constitutively active kinase that is predominantly expressed in testis. In the present study, recombinant GST-SRPK1 was used as substrate to identify potential protein kinase(s) in testis extracts, involved in phosphorylating and thereby regulating the activity of this enzyme. Using a panel of chromatography media, inhibition by heparin, immunoblot analysis, and phosphopeptide mapping, CK2 was determined to be

the major kinase that phosphorylates SRPK1. Phosphorylation of SRPK1 by CK2 occurred mainly at Ser(51) and Ser(555) in vitro, and resulted in approximately 6-fold activation of the enzyme. These findings suggest that SRPK1 may be an important cellular target for CK2 action.

L4 ANSWER 13 OF 62 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:766802 HCAPLUS
DOCUMENT NUMBER: 139:304953
TITLE: Glucose and galactose regulate intestinal absorption of cholesterol
AUTHOR(S): Play, Barbara; Salvini, Severine; Haikal, Ziad; Charbonnier, Monique; Harbis, Amandine; Roussel, Magali; Lairon, Denis; Jourdheuil-Rahmani, Dominique
CORPORATE SOURCE: Faculte de Medecine, UMR-U 476-INSERM (Human Nutrition and Lipids, National Institute for Health and Medical Research), Universite de la Mediterrannee, Marseille, 13385, Fr.
SOURCE: Biochemical and Biophysical Research Communications (2003), 310(2), 446-451
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A dose-dependent increase in cholesterol absorption was induced by glucose addition (0-75 mM) to the apical medium of TC7 cells, a well-characterized clone of Caco-2. The uptake into the cells and the secretion rate to the basolateral space were both enhanced by glucose and galactose. This up-regulation was suppressed by SGLT1 inhibition but not by GLUT2 inhibition. Cholesterol cell uptake was significantly decreased by PMA and increased by chelerythrine, with more pronounced changes in the presence of hexoses. Thus, the involvement of a protein kinase C signalling pathway was evidenced in the regulation processes of intestinal cholesterol absorption. In the presence of antibodies directed to hSR-BI, cholesterol absorption was reduced by 40% and glucose or galactose no longer enhanced it. We suggest that glucose or galactose, through an interaction with SGLT1, activates a protein kinase C pathway that regulates the activity of one of the intestinal cholesterol transporters, namely hSR-BI.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 62 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:639492 SCISEARCH
THE GENUINE ARTICLE: 702JN
TITLE: Anticancer drug resistance induced by disruption of the Saccharomyces cerevisiae NPR2 gene: a novel component involved in cisplatin- and doxorubicin-provoked cell kill
AUTHOR: Schenk P W; Brok M; Boersma A W M; Brandsma J A; Den Dulk H; Burger H; Stoter G; Brouwer J; Nooter K (Reprint)
CORPORATE SOURCE: Erasmus Univ, Med Ctr Rotterdam, Josephine Nefkens Inst, Dept Med Oncol, Sect Expt Chemotherapy, Josephine Nefkens Bldg, Room BE422, POB 1738, NL-3000 DR Rotterdam, Netherlands (Reprint); Erasmus Univ, Med Ctr Rotterdam, Josephine Nefkens Inst, Dept Med Oncol, Sect Expt Chemotherapy, NL-3000 DR Rotterdam, Netherlands; Leiden Univ, Leiden Inst Chem, Gorlaeus Labs, Dept Mol Genet, Med Genet Ctr SW Netherlands, NL-2300 RA Leiden, Netherlands
COUNTRY OF AUTHOR: Netherlands
SOURCE: MOLECULAR PHARMACOLOGY, (AUG 2003) Vol. 64, No. 2, pp. 259-268.
Publisher: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA.

ISSN: 0026-895X.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The therapeutic potential of antitumor drugs is seriously limited by the manifestation of cellular drug resistance. We used the budding yeast Saccharomyces cerevisiae as a model system to identify novel mechanisms of resistance to one of the most active anticancer agents, cisplatin. We pinpointed NPR2 (nitrogen permease regulator 2) as a gene whose disruption conferred resistance to cisplatin. In addition, we observed a 4-fold cross-resistance of yeast npr2Delta cells (i.e., cells from which the NPR2 gene had been disrupted) to the anticancer drug doxorubicin, in combination with hypersensitivity to cadmium chloride. Furthermore, npr2Delta cells displayed unaltered cellular cisplatin and doxorubicin accumulation and showed an enhanced rate of spontaneous mutation compared with the isogenic parent. These data indicate that the npr2Delta phenotype overlaps that of the sky1Delta cells that we characterized previously (Mol Pharmacol 61:659-666, 2002). Therefore, we generated yeast npr2Delta sky1Delta double-knockout cells and performed clonogenic survival assays for cisplatin and doxorubicin, which revealed that NPR2 and SKY1 (**SR**-protein-specific **kinase** from budding yeast) are epistatic. The double-knockout strain was just as resistant to cisplatin and doxorubicin as the single-knockout strain that was most resistant to either drug. In conclusion, we identified NPR2 as a novel component involved in cell kill provoked by cisplatin and doxorubicin, and our data support the hypothesis that NPR2 and SKY1 may use mutual regulatory routes to mediate the cytotoxicity of these anticancer drugs.

L4 ANSWER 15 OF 62 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:631382 HCAPLUS
TITLE: Activation of SR proteins by phosphorylation
AUTHOR(S): Adams, Joseph
CORPORATE SOURCE: Department of Pharmacology, University of California San Diego, La Jolla, CA, 92093-0657, USA
SOURCE: Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), COMP-222. American Chemical Society: Washington, D. C.
CODEN: 69EKY9
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB Both the assembly and selection of splice sites in the spliceosome relies on the participation of protein factors known as SR proteins. These splicing factors, named for their large arginine-serine dipeptide repeats, are activated through phosphorylation by a class of enzymes known as **SR** protein **kinases** [SRPKs]. The SRPKs are highly unique members of the protein kinase family and are distinguished by a large domain insert (approx. 250 a.a.) that bifurcates the canonical kinase domain. Although the domain insert lies near the domain linker region, it does not influence nucleotide binding. We showed that the yeast SRPK, Sky1p, phosphorylates the SR protein, Npl3, at a single site using a typical protein kinase pathway in which slow product release controls substrate turnover. This simple process is juxtaposed by more complex systems where multiple serines are modified. For example, the **human** splicing factor, ASF/SF2, is phosphorylated at 9 serines by SRPK1. Using a start-trap experiment, we showed that SRPK1 phosphorylates these serines without dissociating from ASF/SF2. Thus, SRPK1 is a fully processive protein kinase that -locks' the splicing factor in place and pulls the stretch of serines into the active site. This novel mode of splicing factor activation offers significant catalytic advantage over a distributive mechanism where phospho-intermediates are released after each round of catalysis.

L4 ANSWER 16 OF 62 MEDLINE on STN
ACCESSION NUMBER: 2003056108 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12565823
TITLE: The kic1 kinase of schizosaccharomyces pombe is a CLK/STY orthologue that regulates cell-cell separation.
AUTHOR: Tang Zhaohua; Mandel Linda L; Yean Shyue-Lee; Lin Cindy X; Chen Tina; Yanagida Mitsuhiro; Lin Ren-Jang
CORPORATE SOURCE: Division of Molecular Biology, Beckman Research Institute of the City of Hope, Duarte, CA 91010, USA.
CONTRACT NUMBER: 1 S10 RR01462-01 (NCRR)
SOURCE: Experimental cell research, (2003 Feb 1) 283 (1) 101-15.
Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030205
Last Updated on STN: 20030313
Entered Medline: 20030312

AB The CLK/STY kinases are a family of dual-specificity protein kinases implicated in the regulation of cellular growth and differentiation. Some of the kinases in the family are shown to phosphorylate serine-arginine-rich splicing factors and to regulate pre-mRNA splicing. However, the actual cellular mechanism that regulates cell growth, differentiation, and development by CLK/STY remains unclear. Here we show that a functionally conserved CLK/STY kinase exists in Schizosaccharomyces pombe, and this orthologue, called Kic1, regulates the cell surface and septum formation as well as a late step in cytokinesis. The Kic1 protein is modified in vivo, likely by phosphorylation, suggesting that it can be involved in a control cascade. In addition, kic1(+) together with dsk1(+), which encodes a related **SR**-specific protein **kinase**, constitutes a critical in vivo function for cell growth. The results provide the first in vivo evidence for the functional conservation of the CLK/STY family through evolution from fission yeast to mammals. Furthermore, since cell division and cell-cell interaction are fundamental for the differentiation and development of an organism, the novel cellular role of kic1(+) revealed from this study offers a clue to the understanding of its counterparts in higher eukaryotes.

L4 ANSWER 17 OF 62 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2003148292 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12615334
TITLE: An early ancestor in the evolution of splicing: a Trypanosoma cruzi serine-arginine-rich protein (TcSR) is functional in cis-splicing.
AUTHOR: Portal Daniel; Espinosa Joaquin M; Lobo Guillermo S; Kadener Sebastian; Pereira Claudio A; De La Mata Manuel; Tang Zhaohua; Lin Ren-Jang; Kornblihtt Alberto R; Baralle Francisco E; Flawia Mirtha M; Torres Hector N
CORPORATE SOURCE: Facultad de Ciencias Exactas y Naturales, Instituto de Investigaciones en Ingenieria Genetica y Biologia Molecular, Consejo Nacional de Investigaciones Cientificas y Tecnicas, Universidad de Buenos Aires, Buenos Aires, Argentina.
SOURCE: Molecular and biochemical parasitology, (2003 Mar) 127 (1) 37-46.
Journal code: 8006324. ISSN: 0166-6851.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030401
Last Updated on STN: 20030713
Entered Medline: 20030711

AB A novel serine-arginine-rich protein designated TcSR was identified in Trypanosoma cruzi. The deduced amino acid sequence reveals that TcSR is a member of the SR protein family of splicing factors that contains two RNA-binding domains at the N-terminal side and several serine-arginine repeats at the COOH-terminus. Over expression of either TcSR or the **human** SR-protein associated splicing factor/splicing factor 2 (ASF/SF2) in wild-type Schizosaccharomyces pombe, provoked an elongated phenotype similar to that of fission yeast over expressing the SR-containing splicing factor Prp2, a U2AF(65) orthologue. When a double mutant strain lacking two **SR** protein-specific protein **kinases** was used, expression of TcSR or **human** SR ASF/SF2 splicing factor reverted the mutant to a wild-type phenotype. Transient expression of TcSR in HeLa cells stimulated the inclusion of the EDI exon of **human** fibronectin in an in vivo functional alternative cis-splicing assay. Inclusion was dependent on a splicing enhancer sequence present in the EDI exon. In addition, TcSR and peptides carrying TcSR-RS domain sequences were phosphorylated by a **human** **SR** protein **kinase**. These results indicate that TcSR is a member of the SR splicing network and that some components common to the trans- and cis-splicing machineries evolved from the early origins of the eukaryotic lineage.

L4 ANSWER 18 OF 62 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2003148290 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12615332
TITLE: Trypanosoma cruzi TcSRPK, the first protozoan member of the SRPK family, is biochemically and functionally conserved with metazoan **SR** protein-specific **kinases**
.
AUTHOR: Portal Daniel; Lobo Guillermo S; Kadener Sebastian; Prasad Jayendra; Espinosa Joaquin M; Pereira Claudio A; Tang Zhaohua; Lin Ren-Jang; Manley James L; Kornblihtt Alberto R; Flawia Mirtha M; Torres Hector N
CORPORATE SOURCE: Facultad de Ciencias Exactas y Naturales, Instituto de Investigaciones en Ingenieria Genetica y Biologia Molecular, Consejo Nacional de Investigaciones Cientificas y Tecnicas, Universidad de Buenos Aires, Buenos Aires, Argentina.
SOURCE: Molecular and biochemical parasitology, (2003 Mar) 127 (1) 9-21.
Journal code: 8006324. ISSN: 0166-6851.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030401
Last Updated on STN: 20030713
Entered Medline: 20030711

AB A novel **SR** protein-specific **kinase** (SRPK) from the SRPK family was identified for the first time in a protozoan organism. The primary structure of the protein, named TcSRPK, presents a significant degree of identity with other metazoan members of the family. In vitro phosphorylation experiments showed that TcSRPK has the same substrate specificity relative to other SRPKs. TcSRPK was able to generate a mAb104-recognized phosphoepitope, a SRPK landmark. Expression of TcSRPK in different Schizosaccharomyces pombe strains lead to conserved phenotypes, indicating that TcSRPK is a functional homologue of metazoan

SRPKs. In functional alternative splicing assays in vivo in HeLa cells, TcSRPK enhanced SR protein-dependent inclusion of the EDI exon of the fibronectin minigene. When tested in vitro, it inhibited splicing either on nuclear extracts or on splicing-deficient S100 extracts complemented with ASF/SF2. This inhibition was similar to that observed with **human** SRPK1. This work constitutes the first report of a member of this family of proteins and the existence of an SR-network in a protozoan organism. The implications in the origins and control of splicing are discussed.

L4 ANSWER 19 OF 62 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
DUPLICATE 10
ACCESSION NUMBER: 2003-03137 BIOTECHDS
TITLE: New **SR** protein-specific **kinase** 2 peptides and nucleic acid sequences, useful as models for developing **human** therapeutic targets, in identifying therapeutic proteins, and in identifying agents that modulate kinase activity;
recombinant enzyme protein production and sense and antisense use in gene therapy
AUTHOR: ABU-THREIDEH J; GONG F; KETCHUM K A; DI FRANCESCO V; BEASLEY E M
PATENT ASSIGNEE: ABU-THREIDEH J; GONG F; KETCHUM K A; DI FRANCESCO V; BEASLEY E M
PATENT INFO: US 2002094560 18 Jul 2002
APPLICATION INFO: US 2001-759359 16 Jan 2001
PRIORITY INFO: US 2001-759359 16 Jan 2001; US 2001-759359 16 Jan 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-681805 [73]
AB DERWENT ABSTRACT:
NOVELTY - An isolated **human** kinase peptide, is new.
DETAILED DESCRIPTION - An isolated **human** kinase peptide, comprising or consisting of: (a) a fully defined sequence of 699 amino acids (I) given in the specification; (b) an allelic variant or an ortholog of (I) encoded by a nucleic acid that hybridizes under stringent conditions to the opposite strand of a nucleic acid having a sequence of 3253 (II) or 90541 (III) bp given in the specification; or (c) a fragment of (I) comprising at least 10 contiguous amino acids. INDEPENDENT CLAIMS are also included for the following: (1) an isolated antibody that selectively binds to the peptide; (2) an isolated nucleic acid molecule consisting or comprising: (a) a nucleotide sequence encoding (I); (b) a nucleotide sequence that encodes an allelic variant or ortholog of (I) and that hybridizes under stringent conditions to the opposite strand of (II) or (III); (c) a nucleotide sequence that encodes a fragment of (I) comprising at least 10 contiguous amino acids; (d) a complement of (a)-(c); (3) a gene chip comprising the nucleic acid; (4) a transgenic non-**human** animal comprising the nucleic acid; (5) a nucleic acid vector comprising the nucleic acid; (6) a host cell containing the nucleic acid vector; (7) a method for producing the peptide defined above by introducing a nucleotide sequence encoding an amino acid sequence defined above into a host cell, and culturing the host cell under conditions in which the peptides are expressed from the nucleotide sequence; (8) a method for detecting the presence of a nucleic acid molecule as defined above, in a sample, by contacting the sample with an oligonucleotide that hybridizes to the nucleic acid molecule under stringent conditions, and determining whether the oligonucleotide binds to the nucleic acid molecule in the sample; (9) a method for identifying a modulator of a peptide defined above with an agent, and determining if the agent has modulated the function or activity of the peptide; (10) a method for identifying an agent that binds to a peptide defined above, by contacting the peptide with an agent and assaying the contacted mixture to determine whether a complex is formed with the agent bound to the

peptide; (11) a pharmaceutical composition comprising an agent identified by the method of (10), and a pharmaceutical carrier; (12) a method of treating a disease or condition mediated by a **human** kinase protein by administering an agent identified in (10); (13) a method for identifying a modulator of the expression of a peptide defined above, by contacting the cell expressing the peptide with an agent, and determining if the agent has modulated the expression of the peptide; (14) an isolated **human** kinase peptide having an amino acids sequence that shares at least 70% homology with (I); and (15) an isolated nucleic acid molecule encoding a **human** kinase peptide and sharing at least 80% homology with (II) or (III).

BIOTECHNOLOGY - Preparation: The peptides are isolated from cells by standard isolation techniques. Preferred Method: The agent is administered to a host cell comprising an expression vector that expresses the peptide. Preferred Sequence: The **human** kinase peptide preferably shares at least 90% homology with (I). The nucleic acid encoding the **human** kinase peptide preferably shares at least 90% homology with (II) or (III).

USE - The **SR** protein-specific **kinase** 2 peptide and nucleic acid sequences can be used as models for the development of **human** therapeutic targets, aid in the identification of therapeutic proteins, and as targets for the development of **human** therapeutic agents that modulate kinase activity in cells and tissues that express the kinase. These may further be used as query sequences to perform a search against sequence databases to identify other family members or related sequences. The peptides can also be used to raise antibodies or to elicit another immune response, as markers for tissues in which the corresponding protein is preferentially expressed, to identify the binding partner/ligand to develop a system to identify inhibitors of the binding interaction, and in pharmacogenomic analysis. The nucleic acids are useful as probes or primers, for expressing antigenic portions of the proteins, for constructing vectors, host cells or transgenic animals expressing the nucleic acids and peptide, for monitoring the effectiveness of modulating compounds on the expression or activity of the kinase gene in clinical trials or in treatment regimen, and as antisense constructs to control kinase gene expression.

EXAMPLE - No example given. (56 pages)

L4 ANSWER 20 OF 62 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
DUPLICATE 11

ACCESSION NUMBER: 2002-19513 BIOTECHDS
TITLE: New polypeptide **SR** protein specific serine **kinase** 17.49 and encoding polynucleotides for treating malignant tumors, inflammations, immunological diseases, hemopathy and **human** immunodeficiency virus infection;
vector-mediated recombinant protein gene transfer and expression in host cell for use in cancer and HIV virus infection therapy
AUTHOR: MAO Y; XIE Y
PATENT ASSIGNEE: BODE GENE DEV CO LTD SHANGHAI
PATENT INFO: CN 1347993 8 May 2002
APPLICATION INFO: CN 2000-125676 11 Oct 2000
PRIORITY INFO: CN 2000-125676 11 Oct 2000
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
OTHER SOURCE: WPI: 2002-549000 [59]
AB DERWENT ABSTRACT:

NOVELTY - The present invention discloses one new kind of polypeptide, **SR** protein specific serine **kinase** 17.49, polynucleotides encoding this polypeptide and DNA recombination process to produce the polypeptide. The present invention also discloses the method of applying the polypeptide in treating various diseases, such as

malignant tumors, inflammations, immunological diseases, hemopathy and **human** immunodeficiency virus infection. The present invention also discloses the antagonist resisting the polypeptide and its treatment effect. The present invention also discloses the application of the polynucleotides encoding **SR** protein specific serine **kinase** 17.49.

L4 ANSWER 21 OF 62 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-12412 BIOTECHDS
TITLE: **SR** protein specificity serine **kinase** 212.98 and encoding polynucleotide, used in diagnosis and treatment of malignant tumors, hemopathy, **human** immunodeficiency virus infection, immunological diseases and inflammation;
antibody, DNA primer, DNA probe, DNA microarray, DNA chip, antisense, mimic, agonist, antagonist and inhibitor drug screening, useful for gene therapy, diagnosis and peptide fingerprinting
AUTHOR: MAO Y; XIE Y
PATENT ASSIGNEE: SHANGHAI BIOWINDOW GENE DEV INC
PATENT INFO: WO 2002026791 4 Apr 2002
APPLICATION INFO: WO 2000-CN1069 30 Jun 2000
PRIORITY INFO: CN 2000-116940 30 Jun 2000
DOCUMENT TYPE: Patent
LANGUAGE: German
OTHER SOURCE: WPI: 2002-292474 [33]
AB DERWENT ABSTRACT:
NOVELTY - An isolated polypeptide (I) of **SR** protein specificity serine **kinase** 212.98 containing a 118 residue amino acid sequence (S1), fully defined in the specification, or its fragment, analog or derivative, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) an isolated polynucleotide (II): (a) encoding (S1), or its fragment, analog or derivative; (b) complementary to (a); or (c) not less than 70 % homologous to (a) or (b); (2) a recombinant vector (III) containing an exogenous polynucleotide constructed from (II) and a plasmid, virus vector-expressing vector;(3) a genetically-modified host cell (IV) comprising (II) or (III); (4) producing (I) by culturing (IV) before isolating the product; (5) an antibody that specifically binds (I); (6) mimics or regulators of (I) activity or expression, preferably compounds that can mimic, promote, antagonize or inhibit **SR** protein specificity serine **kinase** 212.98; (7) using the compounds of (6) for regulating (I) in vivo or in vitro; (8) detecting diseases relating to the novel polypeptide or disease susceptibility, by measuring the expression dose of (I), determining (I) activity, or detecting (I) expression dose caused by the polynucleotide that has abnormal activity due to a (II) mutation; (9) using (I) for screening mimics, agonists, antagonists or inhibitors, or for use in peptide fingerprinting identification; (10) using (II) as a primer for nucleic acid amplification reaction or as a probe for hybridization reaction, or in producing gene chips or microarrays; and (11) drug compositions for diseases relating to the (I) containing (I), (II), or mimics, agonists, antagonists, or inhibitors and their preparation in safe amounts with pharmaceutically-acceptable carrier, which can be used as diagnostics as well.

BIOTECHNOLOGY - Preferred Polypeptide: (I) is particularly one with not less than 95 % homology to (S1), especially one with an amino-acid sequence of (S1). Preferred Polynucleotide: (II) encodes the polypeptide of (S1), and contains a sequence with bases 316-672, or bases 1-2410 of a 2410 nucleotide sequence (S2), fully defined in the specification. Preferred Compound: The compound is particularly a polynucleotide of (S2), or an antisense of its fragment.

ACTIVITY - Cytostatic; hemostatic; virucide; immunomodulatory;

antiinflammatory. No supporting data is given. No biological data is given.

MECHANISM OF ACTION - Gene therapy.

USE - (I) and (II) are used in diagnosis and treatment of malignant tumor, hemopathy, **human** immunodeficiency virus (HIV) infection, immunological diseases and various inflammations (claimed).

ADMINISTRATION - Administration is non-oral, particularly by injection. No dosage is suggested.

EXAMPLE - Cloning of **SR** protein specificity serine **kinase** 212.98 was performed by using **human** fetal RNA and then further studies were carried out.(40 pages)

L4 ANSWER 22 OF 62 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:946580 HCAPLUS
DOCUMENT NUMBER: 138:20579
TITLE: **SR** protein-specific **kinases** (SRPKs) as modifiers of the p53 pathway and uses thereof in diagnosis, therapy and drug screening
INVENTOR(S): Friedman, Lori; Plowman, Gregory D.; Belvin, Marcia; Francis-Lang, Helen; Li, Danxi; Funke, Roel P.
PATENT ASSIGNEE(S): Exelixis, Inc., USA
SOURCE: PCT Int. Appl., 137 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 46
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002099427	A1	20021212	WO 2002-US17525		20020603
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2002192695	A1	20021219	US 2002-161510		20020603
US 2003013144	A1	20030116	US 2002-161398		20020603
US 2003036076	A1	20030220	US 2002-160758		20020603
US 2003165809	A1	20030904	US 2002-161565		20020603
PRIORITY APPLN. INFO.:			US 2001-296076P	P	20010605
			US 2001-328605P	P	20011010
			US 2002-357253P	P	20020215

AB The invention has designed genetic screens to identify modifiers of the p53 pathway in Drosophila in which p53 was overexpressed in the wing. In a screen designed to identify enhancers and suppressors of Drosophila p53, homozygous females carrying two copies of p53 have been crossed to 5663 males carrying random insertions of a piggyBac transposon. Progeny containing insertions have been compared to non-insertion-bearing sibling progeny for enhancement or suppression of the p53 phenotypes. Sequence information surrounding the piggyBac insertion site has been used to identify the modifier genes. Modifiers of the wing phenotype have been identified as members of the p53 pathway. The CG8147 gene, which is an enhancer of the wing phenotype, has been identified as a modifier of the p53 pathway. Accordingly, vertebrate orthologs of these modifiers, and preferably the **human** orthologs, **SR** protein-specific **kinase** (SRPK) genes are attractive drag targets for the treatment of pathologies

associated with a defective p53 signaling pathway, such as cancer. The invention also provides methods for utilizing these p53 modifier genes and polypeptides to identify candidate therapeutic agents that can be used in the treatment of disorders associated with defective p53 function.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 62 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:794454 HCAPLUS
DOCUMENT NUMBER: 137:274059
TITLE: Protein and cDNA sequences of **human** serine/arginine-rich protein specific serine kinase 212.98 and therapeutical uses
INVENTOR(S): Mao, Yumin; Xie, Yi
PATENT ASSIGNEE(S): Bode Gene Development Co., Ltd., Shanghai, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 34 pp. CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1331319	A	20020116	CN 2000-116940	20000630
WO 2002026791	A1	20020404	WO 2001-CN1069	20010629

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: CN 2000-116940 A 20000630
AB The invention provides the protein and cDNA sequences of a novel **human** serine/arginine-rich protein (**SR** protein) specific serine **kinase** 212.98 with the mol. weight of 13 kilodaltons cloned from **human** fetal brain. In particular, the invention discloses that the gene encoding this protein has a similar gene expression pattern with gene encoding **SR** protein specific serine **kinase**. The invention also relates to construction of serine/arginine-rich protein specific serine kinase 212.98 expression vector for preparation of recombinant protein using prokaryotes or eukaryotes. The invention relates to preparation of antibody against this protein. The invention further relates to the PCR primers, nucleic acid probes, DNA fragments and protein agonists or antagonists specific for this gene or gene product for the diagnosis as well as treatment of various diseases, such as tumors, blood diseases, HIV infections, immune disorders, inflammations and development disorders.

L4 ANSWER 24 OF 62 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 2002179460 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11792700
TITLE: High density lipoprotein binding to scavenger receptor, Class B, type I activates endothelial nitric-oxide synthase in a ceramide-dependent manner.
AUTHOR: Li Xiang-An; Titlow William B; Jackson Brian A; Giltiay Nathalia; Nikolova-Karakashian Mariana; Uittenbogaard Annette; Smart Eric J

CORPORATE SOURCE: Department of Physiology, University of Kentucky Medical School, Lexington, Kentucky 40536-0230.
CONTRACT NUMBER: HL58475 (NHLBI)
HL62844 (NHLBI)
HL64056 (NHLBI)
P20 RR15592 (NCRR)
SOURCE: Journal of biological chemistry, (2002 Mar 29) 277 (13) 11058-63. Electronic Publication: 2002-01-15.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020326
Last Updated on STN: 20030105
Entered Medline: 20020510

AB Recently it has been demonstrated that high density lipoprotein (HDL) binding to scavenger receptors, class B, type I (SR-BI) stimulates endothelial nitric-oxide synthase (eNOS) activity. In the present studies we used a Chinese hamster ovary cell system and a **human** microvascular endothelial cell line to confirm that HDL stimulates eNOS activity in a SR-BI-dependent manner. Importantly, we have extended these studies to examine the mechanism whereby HDL binding to SR-BI stimulates eNOS. eNOS can be stimulated by an increase in intracellular calcium, by phosphorylation by Akt kinase, or by an increase in intracellular ceramide. Calcium imagining studies and experiments with the calcium chelator, 1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid tetra(acetoxymethyl) ester demonstrated that HDL binding to SR-BI does not induce an increase in intracellular calcium. Antibodies specific for activated Akt kinase demonstrated that HDL binding to **SR**-BI does not induce Akt **kinase** activation. However, HDL binding to SR-BI caused a reversible increase in intracellular ceramide levels from 97 +/- 14 pmol/mg of protein to 501 +/- 21 pmol/mg of protein. In addition, C(2)-ceramide stimulated eNOS to the same extent as HDL, whereas C(2)-dihydroceramide did not stimulate eNOS. We conclude that HDL binding to SR-BI stimulates eNOS by increasing intracellular ceramide levels and is independent of an increase in intracellular calcium or Akt kinase phosphorylation.

L4 ANSWER 25 OF 62 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 2002385243 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12134018
TITLE: Identification of SRPK1 and SRPK2 as the major cellular protein kinases phosphorylating hepatitis B virus core protein.
AUTHOR: Daub Henrik; Blencke Stephanie; Habenberger Peter; Kurtenbach Alexander; Dennenmoser Julia; Wissing Josef; Ullrich Axel; Cotten Matt
CORPORATE SOURCE: Axxima Pharmaceuticals AG, 82152 Martinsried, Germany.. daub@axxima.com
SOURCE: Journal of virology, (2002 Aug) 76 (16) 8124-37.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020723
Last Updated on STN: 20020824
Entered Medline: 20020823

AB Phosphorylation of hepatitis B virus (HBV) core protein has recently been shown to be a prerequisite for pregenomic RNA encapsidation into viral

capsids, but the host cell kinases mediating this essential step of the HBV replication cycle have not been identified. We detected two kinases of 95 and 115 kDa in HuH-7 total cell lysates which interacted specifically with the HBV core protein and phosphorylated its arginine-rich C-terminal domain. The 95-kDa kinase was purified and characterized as **SR** protein-specific **kinase** 1 (SRPK1) by mass spectrometry. Based on this finding, the 115-kDa kinase could be identified as the related kinase SRPK2 by immunoblot analysis. In vitro, both SRPKs phosphorylated HBV core protein on the same serine residues which are found to be phosphorylated in vivo. Moreover, the major cellular HBV core kinase activity detected in the total cell lysate showed biochemical properties identical to those of SRPK1 and SRPK2, as examined by measuring binding to a panel of chromatography media. We also clearly demonstrate that neither the cyclin-dependent kinases Cdc2 and Cdk2 nor protein kinase C, previously implicated in HBV core protein phosphorylation, can account for the HBV core protein kinase activity. We conclude that both SRPK1 and SRPK2 are most likely the cellular protein kinases mediating HBV core protein phosphorylation during viral infection and therefore represent important host cell targets for therapeutic intervention in HBV infection.

L4 ANSWER 26 OF 62 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 2002705381 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12466556
TITLE: PSKH1, a novel splice factor compartment-associated serine kinase.
AUTHOR: Brede Gaute; Solheim Jorun; Prydz Hans
CORPORATE SOURCE: Biotechnology Centre of Oslo, University of Oslo, Gaustadalleen 21, N-0349 Oslo, Norway.
SOURCE: Nucleic acids research, (2002 Dec 1) 30 (23) 5301-9. Journal code: 0411011. ISSN: 1362-4962.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021217
Last Updated on STN: 20021227
Entered Medline: 20021223

AB Small nuclear ribonucleoprotein particles (snRNPs) and non-snRNP splicing factors containing a serine/arginine-rich domain (SR proteins) concentrate in splicing factor compartments (SFCs) within the nucleus of interphase cells. Nuclear SFCs are considered mainly as storage sites for splicing factors, supplying splicing factors to active genes. The mechanisms controlling the interaction of the various spliceosome constituents, and the dynamic nature of the SFCs, are still poorly understood. We show here that endogenous PSKH1, a previously cloned kinase, is located in SFCs. Migration of PSKH1-FLAG into SFCs is enhanced during co-expression of T7-tagged ASF/SF2 as well as other members of the SR protein family, but not by two other non-SR nuclear proteins serving as controls. Similar to the **SR** protein **kinase** family, overexpression of PSKH1 led to reorganization of co-expressed T7-SC35 and T7-ASF/SF2 into a more diffuse nuclear pattern. This redistribution was not dependent on PSKH1 kinase activity. Different from the **SR** protein **kinases**, the SFC-associating features of PSKH1 were located within its catalytic kinase domain and within its C-terminus. Although no direct interaction was observed between PSKH1 and any of the SR proteins tested in pull-down or yeast two-hybrid assays, forced expression of PSKH1-FLAG was shown to stimulate distal splicing of an E1A minigene in HeLa cells. Moreover, a GST-ASF/SF2 fusion was not phosphorylated by PSKH1, suggesting an indirect mechanism of action on SR proteins. Our data suggest a mutual relationship between PSKH1 and SR proteins, as they are able to target PSKH1 into SFCs, while forced PSKH1 expression modulates nuclear dynamics

and the function of co-expressed splicing factors.

L4 ANSWER 27 OF 62 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 2002657611 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12417631
TITLE: **Human** autoimmune sera as molecular probes for the identification of an autoantigen kinase signaling pathway.
AUTHOR: Kamachi Makoto; Le Truc M; Kim Susan J; Geiger Meghan E; Anderson Paul; Utz Paul J
CORPORATE SOURCE: Department of Medicine, Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA 94305, USA.
CONTRACT NUMBER: K08AI01521 (NIAID)
U19-DK61934 (NIDDK)
SOURCE: Journal of experimental medicine, (2002 Nov 4) 196 (9) 1213-25.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021106
Last Updated on STN: 20030110
Entered Medline: 20030109

AB Using **human** autoimmune sera as molecular probes, we previously described the association of phosphorylated serine/arginine splicing factors (SR splicing factors) with the U1-small nuclear ribonucleoprotein (U1-snRNP) and U3-small nucleolar RNP (snoRNP) in apoptotic cells. SR proteins are highly conserved autoantigens whose activity is tightly regulated by reversible phosphorylation of serine residues by at least eight different **SR** protein **kinase kinases** (SRPKs), including SRPK1, SRPK2, and the scleroderma autoantigen topoisomerase I. In this report, we demonstrate that only one of the known SRPKs, SRPK1, is associated with the U1-snRNP autoantigen complex in healthy and apoptotic cells. SRPK1 is activated early during apoptosis, followed by caspase-mediated proteolytic inactivation at later time points. SRPKs are cleaved in vivo after multiple apoptotic stimuli, and cleavage can be inhibited by overexpression of bcl-2 and bcl-x(L), and by exposure to soluble peptide caspase inhibitors. Incubation of recombinant caspases with in vitro-translated SRPKs demonstrates that SRPK1 and SRPK2 are in vitro substrates for caspases-8 and -9, respectively. In contrast, topoisomerase I is cleaved by downstream caspases (-3 and -6). Since each of these SRPKs sits at a distinct checkpoint in the caspase cascade, SRPKs may serve an important role in signaling pathways governing apoptosis, alternative mRNA splicing, SR protein trafficking, RNA stability, and possibly the generation of autoantibodies directed against splicing factors.

L4 ANSWER 28 OF 62 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:524916 HCAPLUS
DOCUMENT NUMBER: 138:163069
TITLE: Effect of inositol hexaphosphate (IP6) on **human** normal and leukaemic hematopoietic cells
AUTHOR(S): Deliliers, Giorgio Lambertenghi; Servida, Federica; Fracchiolla, Nicola S.; Ricci, Clara; Borsotti, Chiara; Colombo, Gualtiero; Soligo, Davide
CORPORATE SOURCE: Bone Marrow Transplantation Unit, I.R.C.C.S., Ospedale Maggiore and University of Milan, Milan, Italy
SOURCE: British Journal of Haematology (2002), 117(3), 577-587
CODEN: BJHEAL; ISSN: 0007-1048
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Inositol hexaphosphate (IP6), a naturally polyphosphorylated carbohydrate, has been reported to have significant in vivo and in vitro anticancer activity against numerous tumors, such as colon, prostate, breast, liver and rhabdomyosarcomas. To confirm this activity in hematol. malignancies and to characterize some of the mechanisms of IP6 action, we analyzed its effects on **human** leukemic cell lines and fresh chronic myelogenous leukemia (CML) progenitor cells using a combined cellular and mol. approach. IP6 had a dose-dependent cytotoxic effect on all of the evaluated cell lines, with accumulation in the G2M phase in two out of five cell lines tested. At the mol. level, cDNA microarray anal. after IP6 exposure showed an extensive down-modulation of genes involved in transcription and cell cycle regulation and a coherent up-regulation of cell cycle inhibitors. Furthermore, IP6 treatment of fresh leukemic samples of bone marrow CD34+ CML progenitor cells significantly inhibited granulocyte-macrophage colony-forming unit (CFU-GM) formation (P = 0.0062) in comparison to normal bone marrow specimens, which were not affected. No differentiating effect on HL60 cells was observed Taken together, our results confirm the antiproliferative activity of IP6 and suggest that it may have a specific antitumor effect also in chronic myeloid leukemias, via active gene modulation.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 29 OF 62 MEDLINE on STN DUPLICATE 16

ACCESSION NUMBER: 2002680617 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12186627
TITLE: Interactions between two fission yeast serine/arginine-rich proteins and their modulation by phosphorylation.
AUTHOR: Tang Zhaohua; Kaufer Norbert F; Lin Ren-Jang
CORPORATE SOURCE: Division of Molecular Biology, Beckman Research Institute of the City of Hope, Duarte, CA 91010, U.S.A.
SOURCE: Biochemical journal, (2002 Dec 1) 368 (Pt 2) 527-34. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021121
Last Updated on STN: 20030118
Entered Medline: 20030117

AB The unexpected low number of genes in the **human** genome has triggered increasing attention to alternative pre-mRNA splicing, and serine/arginine-rich (SR) proteins have been correlated with the complex alternative splicing that is a characteristic of metazoans. SR proteins interact with RNA and splicing protein factors, and they also undergo reversible phosphorylation, thereby regulating constitutive and alternative splicing in mammals and Drosophila. However, it is not clear whether the features of SR proteins and alternative splicing are present in simple and genetically tractable organisms, such as yeasts. In the present study, we show that the SR-like proteins Srp1 and Srp2, found in the fission yeast Schizosaccharomyces pombe, interact with each other and the interaction is modulated by protein phosphorylation. By using Srp1 as bait in a yeast two-hybrid analysis, we specifically isolated Srp2 from a random screen. This Srp interaction was confirmed by a glutathione-S-transferase pull-down assay. We also found that the Srp1-Srp2 complex was phosphorylated at a reduced efficiency by a fission yeast **SR**-specific **kinase**, Dis1-suppression **kinase** (Dsk1). Conversely, Dsk1-mediated phosphorylation inhibited the formation of the Srp complex. These findings offer the first example in fission yeast for interactions between SR-related proteins and the modulation of the interactions by specific protein

phosphorylation, suggesting that a mammalian-like SR protein function may exist in fission yeast.

L4 ANSWER 30 OF 62 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 2002098095 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11827980
TITLE: Disassembly of interchromatin granule clusters alters the coordination of transcription and pre-mRNA splicing.
AUTHOR: Sacco-Bubulya Paula; Spector David L
CORPORATE SOURCE: Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA.
CONTRACT NUMBER: GM 42694 (NIGMS)
SOURCE: Journal of cell biology, (2002 Feb 4) 156 (3) 425-36. Electronic Publication: 2002-02-04.
Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020206
Last Updated on STN: 20030105
Entered Medline: 20020405

AB To examine the involvement of interchromatin granule clusters (IGCs) in transcription and pre-mRNA splicing in mammalian cell nuclei, the serine-arginine (**SR**) protein **kinase** cdc2-like **kinase** (Clk)/STY was used as a tool to manipulate IGC integrity in vivo. Both immunofluorescence and transmission electron microscopy analyses of cells overexpressing Clk/STY indicate that IGC components are completely redistributed to a diffuse nuclear localization, leaving no residual structure. Conversely, overexpression of a catalytically inactive mutant, Clk/STY(K190R), causes retention of hypophosphorylated SR proteins in nuclear speckles. Our data suggest that the protein-protein interactions responsible for the clustering of interchromatin granules are disrupted when SR proteins are hyperphosphorylated and stabilized when SR proteins are hypophosphorylated. Interestingly, cells without intact IGCs continue to synthesize nascent transcripts. However, both the accumulation of splicing factors at sites of pre-mRNA synthesis as well as pre-mRNA splicing are dramatically reduced, demonstrating that IGC disassembly perturbs coordination between transcription and pre-mRNA splicing in mammalian cell nuclei.

L4 ANSWER 31 OF 62 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:455757 BIOSIS
DOCUMENT NUMBER: PREV200200455757
TITLE: Two step transcriptional amplification (TSTA) for enhancing HSV1-sr39tk reporter gene expression using a new single vector feedback strategy.
AUTHOR(S): Iyer, M. [Reprint author]; Zhang, J. L.; Ilagan, R.; Le, K.; Carey, M. F.; Wu, L.; Gambhir, S. S.
CORPORATE SOURCE: Crump Institute for Molecular Imaging, University of California at Los Angeles School of Medicine, Los Angeles, CA, USA
SOURCE: Journal of Nuclear Medicine, (May, 2002) Vol. 43, No. 5 Supplement, pp. 68P. print.
Meeting Info.: 49th Annual Meeting of the Society of Nuclear Medicine. Los Angeles, CA, USA. June 15-19, 2002.
CODEN: JNMEAQ. ISSN: 0161-5505.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Aug 2002

Last Updated on STN: 28 Aug 2002

L4 ANSWER 32 OF 62 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:324915 BIOSIS
DOCUMENT NUMBER: PREV200300324915
TITLE: REGULATION OF GENE ALTERNATIVE SPLICING PATTERNS BY A CYCLIN AND A CDC2 - LIKE KINASE.
AUTHOR(S): Chen, H. H. [Reprint Author]; Sgambato, V.; Fann, M. J. [Reprint Author]
CORPORATE SOURCE: Institute of Neuroscience, National Yang-Ming University, Taipei, Taiwan
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 627.18. http://sfn.scholarone.com. cd-rom.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jul 2003
Last Updated on STN: 16 Jul 2003

AB Alternative splicing is one of the mechanisms that facilitate formation of multiple proteins from single genes. Splicing patterns of neuronal genes are regulated during developmental program and by neuronal activity. We had cloned a putative **SR**-related and CDC2-like protein **kinase**, PKSC, that is predominately expressed in the developing nervous system. PKSC is co-localized with splicing factors (SC35 and SRm300) in nuclear speckles, phosphorylates a splicing factor SF2/ASF in vitro, and therefore may regulate alternative splicing patterns of neuronal genes. When overexpressed in HEK293T cells, PKSC changes the splicing pattern of an E1a reporter gene as analyzed by RT-PCR. This effect was enhanced by Ania-6a60, a cyclin enriched in nuclear speckles, suggesting that Ania-6a60 is an activator of PKSC. Finally, we demonstrated that pksc, like ania-6a, is an immediately early gene up-regulated in the striatum after dopamine or KCl stimulation.

L4 ANSWER 33 OF 62 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:319943 HCAPLUS
DOCUMENT NUMBER: 134:336712
TITLE: Protein and cDNA sequences of a novel **human** cell cycle-regulating protein 53 and diagnostic and therapeutic uses thereof
INVENTOR(S): Mao, Yumin; Xie, Yi
PATENT ASSIGNEE(S): Shanghai Bio Road Gene Development Ltd., Peop. Rep. China
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030833	A1	20010503	WO 2000-CN328	20001016

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,

YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: CN 1999-119816 A 19991022
AB The invention provides protein and cDNA sequences for a novel **human** cell cycle-regulating protein 53, which is a novel member of **SR** protein **kinase** family. The **human** cell cycle-regulating protein 53 gene shares sequence homol. with mouse gene CLK4. The invention also relates to constructs and methods to express the cloned gene for the preparation of its protein and antibodies using E.coli cells or eukaryotic cells, and diagnostic and therapeutic uses for cell cycle-regulating protein 53 related diseases.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 34 OF 62 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:925429 HCAPLUS
DOCUMENT NUMBER: 136:198020
TITLE: p21-activated kinase-1 (PAK1) inhibition of the **human** scavenger receptor class B, type I promoter in macrophages is independent of PAK1 kinase activity, but requires the GTPase-binding domain
AUTHOR(S): Hullinger, Thomas G.; Panek, Robert L.; Xu, Xiangyang; Karathanasis, Sotirios K.
CORPORATE SOURCE: Department of Cardiovascular Pharmacology, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
SOURCE: Journal of Biological Chemistry (2001), 276(50), 46807-46814
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Scavenger receptor class B, type I (SR-BI), is a high d. lipoprotein receptor that mediates the flux of cholesterol between high d. lipoprotein and cells. Recent evidence suggests that SR-BI plays a role in atherosclerosis and that inflammatory mediators down-regulate SR-BI in the macrophage. The purpose of this study was to evaluate the ability of lipopolysaccharide (LPS) to down-regulate the activity of the **human** SR-BI promoter in the macrophage and to delineate the mechanisms involved. Expts. with cultured cells and in vivo derived macrophages showed that LPS has a powerful suppressive effect on SR-BI expression both in vitro and in vivo. Transient transfection studies demonstrated that LPS represses SR-BI promoter activity in the macrophage cell line RAW 264.7. Cotransfection with either a constitutively active p21-activated protein kinase-1 (PAK1) construct (T423E) or a kinase-deficient PAK1 construct (K299R) resulted in repression of the SR-BI promoter, similar to LPS. These results demonstrate that PAK1-mediated down-regulation of the SR-BI promoter is independent of PAK1 kinase activity and suggest that PAK1 mediates the LPS-induced decrease in promoter activity. Cotransfection with constitutively active Cdc42 or Rac expression constructs also resulted in down-regulation of the promoter; whereas the dominant-neg. Cdc42 and Rac constructs elevated basal promoter activity and blunted the LPS response. Cotransfection of PAK1 constructs containing mutations in both the kinase domain and the Cdc42/Rac-binding domain attenuated the PAK1-mediated down-regulation of the promoter, suggesting that Rac and Cdc42 are required for PAK1-mediated decreases in SR-BI promoter activity. 5'-Deletion anal. and gel shift data suggest that LPS inhibits binding of a novel transcription factor to a myeloid zing finger protein-1-like element (-476 to -456) in the **human** SR-BI promoter. These results demonstrate that the PAK1 pathway

down-regulates the SR-BI promoter and suggest that activation of this pathway may play an important role in cholesterol trafficking in the vessel wall.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 35 OF 62 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 2001636611 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11509566
TITLE: Cloning and characterization of an alternatively spliced form of **SR** protein **kinase** 1 that interacts specifically with scaffold attachment factor-B.
AUTHOR: Nikolakaki E; Kohen R; Hartmann A M; Stamm S; Georgatsou E; Giannakouros T
CORPORATE SOURCE: Laboratory of Biochemistry, School of Chemistry, The Aristotelian University of Thessaloniki, Thessaloniki 54006, Greece.. nikol@ccf.auth.gr
SOURCE: Journal of biological chemistry, (2001 Oct 26) 276 (43) 40175-82. Electronic Publication: 2001-08-16. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ224115; GENBANK-AJ318054
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011107
Last Updated on STN: 20030105
Entered Medline: 20011207

AB Serine/arginine protein kinases have been conserved throughout evolution and are thought to play important roles in the regulation of mRNA processing, nuclear import, germline development, polyamine transport, and ion homeostasis. **Human** SRPK1, which was first identified as a kinase specific for the SR family of splicing factors, is located on chromosome 6p21.2-p21.3. We report here the cloning and characterization of SRPK1a, which is encoded by an alternatively processed transcript derived from the SRPK1 gene. SRPK1a contains an insertion of 171 amino acids at its NH(2)-terminal domain and is similar to SRPK1 in substrate specificity and subcellular localization. Moreover, both isoforms can induce alternative splicing of **human** tau exon 10 in transfected cells. Using the yeast two-hybrid assay, we found that the extended NH(2)-terminal domain of SRPK1a interacts with Scaffold Attachment Factor-B, a nuclear scaffold-associated protein. Confirmation of this interaction was provided by in vitro binding assays, as well as by co-immunoprecipitation from 293T cells doubly transfected with SRPK1a and SAF-B. Our studies suggest that different SRPK family members are uniquely regulated and targeted and thus the multiple SRPK kinases present in higher eukaryotes may perform specialized and differentiable functions.

L4 ANSWER 36 OF 62 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 2001511691 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11559564
TITLE: Specific inhibition of serine- and arginine-rich splicing factors phosphorylation, spliceosome assembly, and splicing by the antitumor drug NB-506.
AUTHOR: Pilch B; Allemand E; Facompre M; Bailly C; Riou J F; Soret J; Tazi J
CORPORATE SOURCE: Institut de Genetique Moleculaire, UMR 5535, Centre National de la Recherche Scientifique, IFR 24, Universite de Montpellier II, 34293 Montpellier Cedex, France.
SOURCE: Cancer research, (2001 Sep 15) 61 (18) 6876-84. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010918
Last Updated on STN: 20011015
Entered Medline: 20011011

AB Specific phosphorylation of serine- and arginine-rich pre-mRNA splicing factors (SR proteins) is one of the key determinants regulating splicing events. Several kinases involved in SR protein phosphorylation have been identified and characterized, among which **human** DNA topoisomerase I is known to have DNA-relaxing activity. In this study, we have investigated the mechanism of splicing inhibition by a glycosylated indolocarbazole derivative (NB-506), a potent inhibitor of both kinase and relaxing activities of topoisomerase I. NB-506 completely inhibits the capacity of topoisomerase I to phosphorylate, in vitro, the **human** splicing factor 2/alternative splicing factor (SF2/ASF). This inhibition is specific, because NB-506 does not demonstrate activity against other kinases known to phosphorylate SF2/ASF such as **SR** protein **kinase** 1 and cdc2 **kinase**. Importantly, HeLa nuclear extracts competent in splicing but not splicing-deficient cytoplasmic S100 extracts treated with the drug fail to phosphorylate SF2/ASF and to support splicing of pre-mRNA substrates containing SF2/ASF-target sequences. Native gel analysis of splicing complexes revealed that the drug affects the formation of the spliceosome, a dynamic ribonucleoprotein structure where splicing takes place. In the presence of the drug, neither pre-spliceosome nor spliceosome is formed, demonstrating that splicing inhibition occurs at early steps of spliceosome assembly. Splicing inhibition can be relieved by adding phosphorylated SF2/ASF, showing that extracts treated with NB-506 lack a phosphorylating activity required for splicing. Moreover, NB-506 has a cytotoxic effect on murine P388 leukemia cells but not on P388CPT5 camptothecin-resistant cells that carry two point mutations in conserved regions of topoisomerase I gene (Gly361Val and Asp709Tyr). After drug treatment, P388 cells accumulated hypophosphorylated forms of SR proteins and polyadenylated RNA in the nucleus. In contrast, neither SR protein phosphorylation nor polyadenylated mRNA distribution was affected in P388 CPT5-treated cells. Consistently, NB506 treatment altered the mRNA levels and/or splicing pattern of several tested genes (Bcl-X, CD 44, SC35, and Sty) in P388 cells but not in P388 CPT5 cells. The study shows for the first time that indolocarbazole drugs targeting topoisomerase I can affect gene expression by modulating pre-mRNA splicing through inhibition of SR proteins phosphorylation.

L4 ANSWER 37 OF 62 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 2001276319 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11359904
TITLE: NF-kappaB inducers upregulate cFLIP, a cycloheximide-sensitive inhibitor of death receptor signaling.
AUTHOR: Kreuz S; Siegmund D; Scheurich P; Wajant H
CORPORATE SOURCE: Institute of Cell Biology and Immunology, University of Stuttgart, 70569 Stuttgart, Germany.
SOURCE: Molecular and cellular biology, (2001 Jun) 21 (12) 3964-73. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20020919
Entered Medline: 20010628

AB The caspase 8 homologue FLICE-inhibitory protein (cFLIP) is a potent

negative regulator of death receptor-induced apoptosis. We found that cFLIP can be upregulated in some cell lines under critical involvement of the NF-kappaB pathway, but NF-kappaB activation was clearly not sufficient for cFLIP induction in all cell lines. Treatment of SV80 cells with the proteasome inhibitor N-benzoyloxycarbonyl (Z)-Leu-Leu-leucinal (MG-132) or geldanamycin, a drug interfering with tumor necrosis factor (TNF)-induced NF-kappaB activation, inhibited TNF-induced upregulation of cFLIP. Overexpression of a nondegradable IkappaBalpha mutant (IkappaBalpha-**SR**) or lack of IkappaB **kinase** gamma expression completely prevented phorbol myristate acetate-induced upregulation of cFLIP mRNA in Jurkat cells. These data point to an important role for NF-kappaB in the regulation of the cFLIP gene. SV80 cells normally show resistance to TNF-related apoptosis-inducing ligand (TRAIL) and TNF, as apoptosis can be induced only in the presence of low concentrations of cycloheximide (CHX). However, overexpression of IkappaBalpha-SR rendered SV80 cells sensitive to TRAIL-induced apoptosis in the absence of CHX, and cFLIP expression was able to reverse the proapoptotic effect of NF-kappaB inhibition. Western blot analysis further revealed that cFLIP, but not TRAF1, A20, and cIAP2, expression levels rapidly decrease upon CHX treatment. In conclusion, these data suggest a key role for cFLIP in the antiapoptotic response of NF-kappaB activation.

L4 ANSWER 38 OF 62 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 2001155589 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11158320
TITLE: Distinctive features of Drosophila alternative splicing factor RS domain: implication for specific phosphorylation, shuttling, and splicing activation.
AUTHOR: Allemand E; Gattoni R; Bourbon H M; Stevenin J; Caceres J F; Soret J; Tazi J
CORPORATE SOURCE: Institut de Genetique Moleculaire, UMR5535 du CNRS, IFR 24, F34293 Montpellier Cedex 5, Toulouse, France.
SOURCE: Molecular and cellular biology, (2001 Feb) 21 (4) 1345-59. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010322

AB The **human** splicing factor 2, also called **human** alternative splicing factor (hASF), is the prototype of the highly conserved SR protein family involved in constitutive and regulated splicing of metazoan mRNA precursors. Here we report that the Drosophila homologue of hASF (dASF) lacks eight repeating arginine-serine dipeptides at its carboxyl-terminal region (RS domain), previously shown to be important for both localization and splicing activity of hASF. While this difference has no effect on dASF localization, it impedes its capacity to shuttle between the nucleus and cytoplasm and abolishes its phosphorylation by **SR** protein **kinase** 1 (SRPK1). dASF also has an altered splicing activity. While being competent for the regulation of 5' alternative splice site choice and activation of specific splicing enhancers, dASF fails to complement S100-cytoplasmic splicing-deficient extracts. Moreover, targeted overexpression of dASF in transgenic flies leads to higher deleterious developmental defects than hASF overexpression, supporting the notion that the distinctive structural features at the RS domain between the two proteins are likely to be functionally relevant in vivo.

L4 ANSWER 39 OF 62 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:755374 SCISEARCH
THE GENUINE ARTICLE: 471LG
TITLE: Evidence for a role of Sky1 p-mediated phosphorylation in 3 ' splice involving both Prp8 and site recognition Prp17/Slu4
AUTHOR: Dagher S F; Fu X D (Reprint)
CORPORATE SOURCE: Univ Calif San Diego, Sch Med, Dept Cellular & Mol Med, 9500 Gilman Dr, La Jolla, CA 92093 USA (Reprint); Univ Calif San Diego, Sch Med, Dept Cellular & Mol Med, La Jolla, CA 92093 USA
COUNTRY OF AUTHOR: USA
SOURCE: RNA-A PUBLICATION OF THE RNA SOCIETY, (SEP 2001) Vol. 7, No. 9, pp. 1284-1297.
Publisher: CAMBRIDGE UNIV PRESS, 110 MIDLAND AVE, PORT CHESTER, NY 10573-9863 USA.
ISSN: 1355-8382.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 79

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The SRPK family of kinases is specific for RS domain-containing splicing factors and known to play a critical role in protein-protein interaction and intracellular distribution of their substrates in both yeast and mammalian cells. However, the function of these kinases in pre-mRNA splicing remains unclear. Here we report that SKY1, a SRPK family member in Saccharomyces cerevisiae, genetically interacts with PRP8 and PRP17/SLU4, both of which are involved in splice site selection during pre-mRNA splicing. Prp8 is essential for splicing and is known to interact with both 5' and 3' splice sites in the spliceosomal catalytic center, whereas Prp17/SIu4 is nonessential and is required only for efficient recognition of the 3' splice site. Interestingly, deletion of SKY1 was synthetically lethal with all prp17 mutants tested, but only with specific prp8 alleles in a domain implicated in governing fidelity of 3'AG recognition. Indeed, deletion of SKY1 specifically suppressed 3'AG mutations in ACT1-CUP1 splicing reporters. These results suggest for the first time that 3'AG recognition may be subject to phosphorylation regulation by Sky1p during pre-mRNA splicing.

L4 ANSWER 40 OF 62 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:153060 BIOSIS
DOCUMENT NUMBER: PREV200200153060
TITLE: p210BCR/ABL-induced alteration of mRNA splicing as a potential mechanism of CML pathogenesis.
AUTHOR(S): Salesse, Stephanie [Reprint author]; Dylla, Scott J. [Reprint author]; Verfaillie, Catherine M. [Reprint author]
CORPORATE SOURCE: Stem Cell Institute, University of Minnesota Cancer Center, Minneapolis, MN, USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 144a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Feb 2002
Last Updated on STN: 26 Feb 2002

AB Chronic Myelogenous Leukemia (CML) is a malignancy of the **human** hematopoietic stem cell (HSC) characterized by presence of the BCR/ABL gene and its product, p210BCR/ABL. The exact mechanism(s) underlying

p210BCR/ABL-mediated transformation is not totally understood. Pre-mRNA processing is an important step in the transition from DNA to protein, wherein exons likely require different groups of trans-acting factors and cis-acting elements for their proper union. Although alternative splicing of mRNA is a critical determinant of a cell's protein repertoire, it has never been implicated in CML pathogenesis. Subtractive hybridization techniques comparing MSCV-IRES-GFP and MSCV-p210BCR/ABL-IRES-GFP transduced cord blood (CB) CD34+ cells identified multiple genes involved in pre-mRNA splicing in BCR/ABL-positive cells, including the **SR** -protein **kinase** 1 (SRPK1) and RNA Helicase II/Gu. Northern blot, quantitative real-time PCR, and Western blot analyses have confirmed increased expression of these genes and their products in primary CML versus normal CD34+ cells and p210BCR/ABL versus GFP-transduced CB CD34+ cells. Moreover, the phosphorylation of SRPK1 substrates, such as SR proteins, which are critical components of the spliceosome complex, is increased in p210BCR/ABL-containing cells. Intriguingly, previous experiments in our lab investigating the abnormal adhesion and migration of BCR/ABL-positive cells characterized alternatively splicing of the non-receptor tyrosine kinase gene, PYK2, whose product is intimately involved in beta1-integrin signaling. In p210BCR/ABL-positive cells, the ratio of full-length Pyk2 versus the PYK2 isoform normally predominant in hematopoietic cells, Pyk2H, is increased. Alternative splicing of PYK2 is directly influenced by p210BCR/ABL as indicated by the significantly higher ratio of Pyk2/Pyk2H in primary CML versus normal CD34+ cells and p210BCR/ABL versus GFP-transduced CB CD34+ cells. Moreover, treatment of primary CML CD34+ cells or p210BCR/ABL-transduced CB CD34+ cells with the Abl-specific tyrosine kinase inhibitor, STI571, normalized the Pyk2/Pyk2H ratio. This STI571-induced reversion to normal PYK2 gene splicing correlated with decreased expression of the splicing proteins SRPK1 and RNA Helicase II/Gu, and reduced phosphorylation of the SR proteins. Reversible phosphorylation of SR proteins is critical for spliceosome assembly and subsequent splicing, and SRPK1 overexpression inhibits pre-mRNA splicing (Genes Dev 1996 10:1569). Therefore, experiments are in progress in which SRPK1 is overexpressed in normal CB CD34+ cells, by MSCV-based retroviral transduction, to determine whether the BCR/ABL-induced alteration of PYK2 mRNA splicing is mediated solely by the elevation of SRPK1 expression/activity, and whether these changes in splicing contribute to the abnormal adhesion and migration characteristics observed in CML.

L4 ANSWER 41 OF 62 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 2000211404 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10747030
TITLE: Functional characterization of SR and SR-related genes in Caenorhabditis elegans.
AUTHOR: Longman D; Johnstone I L; Caceres J F
CORPORATE SOURCE: MRC Human Genetics Unit, Western General Hospital, Edinburgh EH4 2XU.
SOURCE: EMBO journal, (2000 Apr 3) 19 (7) 1625-37.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000515

AB The SR proteins constitute a family of nuclear phosphoproteins, which are required for constitutive splicing and also influence alternative splicing regulation. Initially, it was suggested that SR proteins were functionally redundant in constitutive splicing. However, differences have been observed in alternative splicing regulation, suggesting unique

functions for individual SR proteins. Homology searches of the Caenorhabditis elegans genome identified seven genes encoding putative orthologues of the **human** factors SF2/ASF, SRp20, SC35, SRp40, SRp75 and p54, and also several SR-related genes. To address the issue of functional redundancy, we used dsRNA interference (RNAi) to inhibit specific SR protein function during C.elegans development. RNAi with CeSF2/ASF caused late embryonic lethality, suggesting that this gene has an essential function during C.elegans development. RNAi with other SR genes resulted in no obvious phenotype, which is indicative of gene redundancy. Simultaneous interference of two or more SR proteins in certain combinations caused lethality or other developmental defects. RNAi with CeSRPK, an **SR** protein **kinase**, resulted in early embryonic lethality, suggesting an essential role for SR protein phosphorylation during development.

L4 ANSWER 42 OF 62 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000394206 EMBASE
TITLE: Recent developments of rebeccamycin analogues as topoisomerase I inhibitors and antitumor agents.
AUTHOR: Prudhomme M.
CORPORATE SOURCE: M. Prudhomme, Laboratoire de Synthese, Elec.synth. Etud. Syst. Int. Biol., Universite Blaise Pascal, 63177 Aubiere, France. mprud@chimtp.univbpclermont.fr
SOURCE: Current Medicinal Chemistry, (2000) Vol. 7, No. 12, pp. 1189-1212.
Refs: 68
ISSN: 0929-8673 CODEN: CMCHE7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20001213
Last Updated on STN: 20001213

AB DNA topoisomerases are essential for the survival of prokaryotic and eukaryotic organisms. Topoisomerases inhibitors, due to their capacity to induce DNA breaking, can exhibit interesting antitumor properties. While there are many potent antitumor agents which target topoisomerase II, relatively few families of specific topoisomerase I inhibitors have been identified. The present review describes a new family of topoisomerase I inhibitors, analogues of the bacterial metabolite rebeccamycin. These compounds possess an indolocarbazole chromophore onto which is attached a sugar residue. Important structure-activity relationships studies in this series have helped to understand the role of the carbohydrate moiety which is absolutely necessary for topoisomerase I poisoning, the influence of the stereochemistry (α or β) of its linkage to indole, the influence of the functionalities and substitutions on the sugar moiety and on the aromatic framework have been investigated. In addition to their action on DNA, rebeccamycin analogues may inhibit the **SR** **kinase** activity of topoisomerase I and therefore constitute a unique family of topoisomerase I poisons quite different from the well known camptothecins.

L4 ANSWER 43 OF 62 MEDLINE on STN DUPLICATE 23

ACCESSION NUMBER: 2000094960 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10629038
TITLE: Biochemical and genetic conservation of fission yeast Dsk1 and **human SR** protein-specific **kinase** 1.
AUTHOR: Tang Z; Kuo T; Shen J; Lin R J

CORPORATE SOURCE: Department of Molecular Biology, Beckman Research Institute of the City of Hope, Duarte, California 91010, USA.
SOURCE: Molecular and cellular biology, (2000 Feb) 20 (3) 816-24. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB Arginine/serine-rich (RS) domain-containing proteins and their phosphorylation by specific protein kinases constitute control circuits to regulate pre-mRNA splicing and coordinate splicing with transcription in mammalian cells. We present here the finding that similar SR networks exist in Schizosaccharomyces pombe. We previously showed that Dsk1 protein, originally described as a mitotic regulator, displays high activity in phosphorylating S. pombe Prp2 protein (spU2AF59), a homologue of **human** U2AF65. We now demonstrate that Dsk1 also phosphorylates two recently identified fission yeast proteins with RS repeats, Srp1 and Srp2, in vitro. The phosphorylated proteins bear the same phosphoepitope found in mammalian SR proteins. Consistent with its substrate specificity, Dsk1 forms kinase-competent complexes with those proteins. Furthermore, dsk1(+) gene determines the phenotype of prp2(+) overexpression, providing in vivo evidence that Prp2 is a target for Dsk1. The dsk1-null mutant strain became severely sick with the additional deletion of a related kinase gene. Significantly, **human** **SR** protein-specific **kinase** 1 (SRPK1) complements the growth defect of the double-deletion mutant. In conjunction with the resemblance of dsk1(+) and SRPK1 in sequence homology, biochemical properties, and overexpression phenotypes, the complementation result indicates that SRPK1 is a functional homologue of Dsk1. Collectively, our studies illustrate the conserved SR networks in S. pombe consisting of RS domain-containing proteins and **SR** protein-specific **kinases** and thus establish the importance of the networks in eucaryotic organisms.

L4 ANSWER 44 OF 62 MEDLINE on STN DUPLICATE 24
ACCESSION NUMBER: 2000458663 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10952997
TITLE: Conserved **SR** protein **kinase** functions in nuclear import and its action is counteracted by arginine methylation in Saccharomyces cerevisiae.
AUTHOR: Yun C Y; Fu X D
CORPORATE SOURCE: Department of Cellular and Molecular Medicine, University of California at San Diego, La Jolla, California 92093-0651, USA.
SOURCE: Journal of cell biology, (2000 Aug 21) 150 (4) 707-18. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20030207
Entered Medline: 20000928

AB Mammalian serine and arginine-rich (SR) proteins play important roles in both constitutive and regulated splicing, and **SR** protein-specific **kinases** (SRPKs) are conserved from **humans** to yeast. Here, we demonstrate a novel function of the single conserved **SR** protein **kinase** Sky1p in nuclear

import in budding yeast. The yeast SR-like protein Npl3p is known to enter the nucleus through a composite nuclear localization signal (NLS) consisting of a repetitive arginine- glycine-glycine (RGG) motif and a nonrepetitive sequence. We found that the latter is the site for phosphorylation by Sky1p and that this phosphorylation regulates nuclear import of Npl3p by modulating the interaction of the RGG motif with its nuclear import receptor Mtr10p. The RGG motif is also methylated on arginine residues, but methylation does not affect the Npl3p-Mtr10p interaction in vitro. Remarkably, arginine methylation interferes with Sky1p-mediated phosphorylation, thereby indirectly influencing the Npl3p-Mtr10p interaction in vivo and negatively regulating nuclear import of Npl3p. These results suggest that nuclear import of Npl3p is coordinately influenced by methylation and phosphorylation in budding yeast, which may represent conserved components in the dynamic regulation of RNA processing in higher eukaryotic cells.

L4 ANSWER 45 OF 62 MEDLINE on STN
ACCESSION NUMBER: 2000062862 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10593939
TITLE: An SC35-like protein and a novel serine/arginine-rich protein interact with Arabidopsis U1-70K protein.
AUTHOR: Golovkin M; Reddy A S
CORPORATE SOURCE: Department of Biology and Program in Cell and Molecular Biology, Colorado State University, Fort Collins, Colorado 80523, USA.
SOURCE: Journal of biological chemistry, (1999 Dec 17) 274 (51) 36428-38.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
OTHER SOURCE: GENBANK-AF099940; GENBANK-AF151366
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20020121
Entered Medline: 20000127

AB The U1 small nuclear ribonucleoprotein 70-kDa protein, a U1 small nuclear ribonucleoprotein-specific protein, has been shown to have multiple roles in nuclear precursor mRNA processing in animals. By using the C-terminal arginine-rich region of Arabidopsis U1-70K protein in the yeast two-hybrid system, we have identified an SC35-like (SR33) and a novel plant serine/arginine-rich (SR) protein (SR45) that interact with the plant U1-70K. The SR33 and SR45 proteins share several features with SR proteins including modular domains typical of splicing factors in the SR family of proteins. However, both plant SR proteins are rich in proline, and SR45, unlike most animal SR proteins, has two distinct arginine/serine-rich domains separated by an RNA recognition motif. By using coprecipitation assays we confirmed the interaction of plant U1-70K with SR33 and SR45 proteins. Furthermore, in vivo and in vitro protein-protein interaction experiments have shown that SR33 protein interacts with itself and with SR45 protein but not with two other members (SRZ21 and SRZ22) of the SR family that are known to interact with the Arabidopsis full-length U-70K only. A Clk/Sty protein kinase (AFC-2) from Arabidopsis phosphorylated four SR proteins (SR33, SR45, SRZ21, and SRZ22). Coprecipitation studies have confirmed the interaction of **SR** proteins with AFC2 **kinase**, and the interaction between AFC2 and SR33 is modulated by the phosphorylation status of these proteins. These and our previous results suggest that the plant U1-70K interacts with at least four distinct members of the SR family including SR45 with its two arginine/serine-rich domains, and the interaction between the SR proteins and AFC2 is modulated by phosphorylation. The interaction of plant U1-70K with a novel set of proteins suggests the

early stages of spliceosome assembly, and intron recognition in plants is likely to be different from animals.

L4 ANSWER 46 OF 62 MEDLINE on STN DUPLICATE 25
ACCESSION NUMBER: 1999214190 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10196197
TITLE: The subcellular localization of SF2/ASF is regulated by direct interaction with **SR** protein **kinases** (SRPKs).
AUTHOR: Koizumi J; Okamoto Y; Onogi H; Mayeda A; Krainer A R; Hagiwara M
CORPORATE SOURCE: Department of Functional Genomics, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113, Japan.
CONTRACT NUMBER: CA13106 (NCI)
SOURCE: Journal of biological chemistry, (1999 Apr 16) 274 (16) 11125-31.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 20020420
Entered Medline: 19990517

AB Serine/arginine-rich (SR) proteins play an important role in constitutive and alternative pre-mRNA splicing. The C-terminal arginine-serine domain of these proteins, such as SF2/ASF, mediates protein-protein interactions and is phosphorylated in vivo. Using glutathione S-transferase (GST)-SF2/ASF-affinity chromatography, the SF2/ASF kinase activity was co-purified from HeLa cells with a 95-kDa protein, which was recognized by an anti-**SR** protein **kinase** (SRPK) 1 monoclonal antibody. Recombinant SRPK1 and SRPK2 bound to and phosphorylated GST-SF2/ASF in vitro. Phosphopeptide mapping showed that identical sites were phosphorylated in the pull-down kinase reaction with HeLa extracts and by recombinant SRPKs. Epitope-tagged SF2/ASF transiently expressed in COS7 cells co-immunoprecipitated with SRPKs. Deletion analysis mapped the phosphorylation sites to a region containing an (Arg-Ser)8 repeat beginning at residue 204, and far-Western analysis showed that the region is required for binding of SRPKs to SF2/ASF. Further binding studies showed that SRPKs bound unphosphorylated SF2/ASF but did not bind phosphorylated SF2/ASF. Expression of an SRPK2 kinase-inactive mutant caused accumulation of SF2/ASF in the cytoplasm. These results suggest that the formation of complexes between SF2/ASF and SRPKs, which is influenced by the phosphorylation state of SF2/ASF, may have regulatory roles in the assembly and localization of this splicing factor.

L4 ANSWER 47 OF 62 MEDLINE on STN DUPLICATE 26
ACCESSION NUMBER: 1999380486 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10390541
TITLE: **SR** protein-specific **kinase** 1 is highly expressed in testis and phosphorylates protamine 1.
AUTHOR: Papoutsopoulou S; Nikolakaki E; Chalepakis G; Kruft V; Chevaillier P; Giannakouros T
CORPORATE SOURCE: Laboratory of Biochemistry, School of Chemistry, The Aristotelian University of Thessaloniki, Thessaloniki 54 006, Greece.
SOURCE: Nucleic acids research, (1999 Jul 15) 27 (14) 2972-80.
Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ224115
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990925
Last Updated on STN: 20020420
Entered Medline: 19990903

AB Arginine/serine protein kinases constitute a novel class of enzymes that can modify arginine/serine (RS) dipeptide motifs. SR splicing factors that are essential for pre-mRNA splicing are among the best characterized proteins that contain RS domains. TwoSRprotein-specifickinases, SRPK1 and SRPK2, have been considered as highly specific for the phosphorylation of these proteins, thereby contributing to splicing regulation. However, despite the fact that SR proteins are more or less conserved among metazoa and have a rather ubiquitous tissue distribution we now demonstrate that SRPK1 is predominantly expressed in testis. In situ expression analysis on transverse sections of adult mouse testis shows that SRPK1 mRNA is abundant in all germinal cells but not in mature spermatozoa. RS kinase activity was found primarily in the cytosol and only minimal activity was detected in the nucleus. In a search for testis-specific substrates of SRPK1 we found that the enzyme phosphorylates **human** protamine 1 as well as a cytoplasmic pool of SR proteins present in the testis. Protamine 1 belongs to a family of small basic arginine-rich proteins that replace histones during the development of mature spermatozoa. The result of this progressive replacement is the formation of a highly compact chromatin structure devoid of any transcriptional activity. These findings indicate that SRPK1 may have a role not only in pre-mRNA splicing, but also in the condensation of sperm chromatin.

L4 ANSWER 48 OF 62 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:594258 HCAPLUS
DOCUMENT NUMBER: 131:320552
TITLE: The casein kinase Iα isoform is both physically positioned and functionally competent to regulate multiple events of mRNA metabolism
AUTHOR(S): Gross, Stefan D.; Loijens, Joost C.; Anderson, Richard A.
CORPORATE SOURCE: Department of Pharmacology, University of Wisconsin Medical School, Madison, WI, USA
SOURCE: Journal of Cell Science (1999), 112(16), 2647-2656
CODEN: JNCSAI; ISSN: 0021-9533
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Casein kinase I is a highly conserved family of serine/threonine protein kinases present in every organism tested from yeast to **humans**. To date, little is known about the function of the higher eukaryotic isoforms in this family. The CKI isoforms in Saccharomyces cerevisiae, however, have been genetically linked to the regulation of DNA repair, cell cycle progression and cytokinesis. It has also been established that the nuclear localization of two of these isoforms is essential for their function. The work presented here demonstrates that the higher eukaryotic CKIα isoform is also present within nuclei of certain established cell lines and associated with discrete nuclear structures. The nature of its nuclear localization was characterized. In this regard, CKIα was shown to colocalize with factors involved in pre-mRNA splicing at nuclear speckles and that its association with these structures exhibited several biochem. properties in common with known splicing factors. The kinase was also shown to be associated with a complex that contained certain splicing factors. Finally, in vitro, CKIα was shown to be capable of phosphorylating particular splicing factors within a region rich in serine/arginine dipeptide repeat motifs suggesting that it has both the opportunity and the capacity to regulate one or more steps of mRNA metabolism

REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 49 OF 62 MEDLINE on STN DUPLICATE 27
ACCESSION NUMBER: 1999146918 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10022843
TITLE: The splicing factor-associated protein, p32, regulates RNA splicing by inhibiting ASF/SF2 RNA binding and phosphorylation.
AUTHOR: Petersen-Mahrt S K; Estmer C; Ohrmalm C; Matthews D A; Russell W C; Akusjarvi G
CORPORATE SOURCE: Department of Medical Biochemistry and Microbiology, BMC, Uppsala University, S-751 23 Uppsala, Sweden.
SOURCE: EMBO journal, (1999 Feb 15) 18 (4) 1014-24.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990426

AB The cellular protein p32 was isolated originally as a protein tightly associated with the essential splicing factor ASF/SF2 during its purification from HeLa cells. ASF/SF2 is a member of the SR family of splicing factors, which stimulate constitutive splicing and regulate alternative RNA splicing in a positive or negative fashion, depending on where on the pre-mRNA they bind. Here we present evidence that p32 interacts with ASF/SF2 and SRp30c, another member of the SR protein family. We further show that p32 inhibits ASF/SF2 function as both a splicing enhancer and splicing repressor protein by preventing stable ASF/SF2 interaction with RNA, but p32 does not block SRp30c function. ASF/SF2 is highly phosphorylated in vivo, a modification required for stable RNA binding and protein-protein interaction during spliceosome formation, and this phosphorylation, either through HeLa nuclear extracts or through specific **SR** protein **kinases**, is inhibited by p32. Our results suggest that p32 functions as an ASF/SF2 inhibitory factor, regulating ASF/SF2 RNA binding and phosphorylation. These findings place p32 into a new group of proteins that control RNA splicing by sequestering an essential RNA splicing factor into an inhibitory complex.

L4 ANSWER 50 OF 62 MEDLINE on STN DUPLICATE 28
ACCESSION NUMBER: 1999160399 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10049757
TITLE: SRPK1 and LBR protein kinases show identical substrate specificities.
AUTHOR: Papoutsopoulou S; Nikolakaki E; Giannakouros T
CORPORATE SOURCE: Laboratory of Biochemistry, School of Chemistry, Aristotelian University of Thessaloniki, Thessaloniki, 54 006, Greece.
SOURCE: Biochemical and biophysical research communications, (1999 Feb 24) 255 (3) 602-7.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990413
Last Updated on STN: 20020420
Entered Medline: 19990401

AB Arginine/serine protein kinases constitute a novel class of enzymes that can modify arginine/serine (RS) dipeptide motifs. SR splicing factors that are essential for pre-mRNA splicing and the lamin B receptor (LBR), an integral protein of the inner nuclear membrane, are among the best characterized proteins that contain RS domains. Two **SR** Protein-specific **Kinases**, SRPK1 and SRPK2, have been shown to phosphorylate specifically the RS motifs of the SR family of splicing factors and play an important role in regulating both the spliceosome assembly and their intranuclear distribution, whereas an LBR-associated kinase, that specifically phosphorylates a stretch of RS repeats located at the NH2-terminal region of LBR, has been recently purified and characterized from turkey erythrocyte nuclear envelopes. Using synthetic peptides representing different regions of LBR and recombinant proteins produced in bacteria we now demonstrate that SRPK1 modifies LBR with similar kinetics and on the same sites as the LBR kinase, that are also phosphorylated in vivo. These data provide significant evidence for a new role of SRPK1 in addition to that of pre-mRNA splicing.

L4 ANSWER 51 OF 62 MEDLINE on STN
ACCESSION NUMBER: 2000012383 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10546892
TITLE: **SR** protein **kinases**: the splice of life.
AUTHOR: Stojdl D F; Bell J C
CORPORATE SOURCE: Ottawa Regional Cancer Centre Research Laboratories, ON, Canada.
SOURCE: Biochemistry and cell biology = Biochimie et biologie cellulaire, (1999) 77 (4) 293-8. Ref: 38
Journal code: 8606068. ISSN: 0829-8211.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991201

AB The eukaryotic genome codes for most of its proteins though discontinuous coding sequences called exons, which are separated by noncoding sequences known as introns. Following transcription of a gene, these exons must be spliced precisely, removing the intervening introns, to form meaningful mature messenger RNAs (mRNA) that are transported to the cytoplasm and translated by the ribosomal machinery. To add yet another level of complexity, a process known as alternative splicing exists, whereby a single pre-mRNA can give rise to two or more mature mRNAs depending on the combination of exons spliced together. Alternative splicing of pre-mRNAs is emerging as an important mechanism for gene regulation in many organisms. The classic example of splicing as a regulator of genetic information during a developmental process is sex determination in Drosophila. The now well-characterized cascade of sex-specific alternative splicing events demonstrates nicely how the control of splice site selection during pre-mRNA processing can have a profound effect on the development of an organism. The factors involved in pre-mRNA splicing and alternative splice site selection have been the subject of active study in recent years. Emerging from these studies is a picture of regulation based on protein-protein, protein-RNA, and RNA-RNA interactions. How the interaction of the various splicing constituents is controlled, however, is still poorly understood. One of the mechanisms of regulation that has received attention recently is that of posttranslational phosphorylation. In the following article, we cite the evidence for a role of phosphorylation in constitutive and alternative

splicing and discuss some of the recent information on the biochemistry and biology of the enzymes involved.

L4 ANSWER 52 OF 62 MEDLINE on STN DUPLICATE 29
ACCESSION NUMBER: 1998158002 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9488736
TITLE: Fission yeast mitotic regulator Dsk1 is an **SR** protein-specific **kinase**.
AUTHOR: Tang Z; Yanagida M; Lin R J
CORPORATE SOURCE: Department of Molecular Biology, Beckman Research Institute of the City of Hope, Duarte, California 91010, USA.
SOURCE: Journal of biological chemistry, (1998 Mar 6) 273 (10) 5963-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980416
Last Updated on STN: 20020420
Entered Medline: 19980407

AB Intricate interplay may exist between pre-mRNA splicing and the cell division cycle, and fission yeast Dsk1 appears to play a role in such a connection. Previous genetic analyses have implicated Dsk1 in the regulation of chromosome segregation at the metaphase/anaphase transition. Yet, its protein sequence suggests that Dsk1 may function as a kinase specific for SR proteins, a family of pre-mRNA splicing factors containing arginine-serine repeats. Using an in vitro system with purified components, we showed that Dsk1 phosphorylated **human** and yeast SR proteins with high specificity. The Dsk1-phosphorylated SF2/ASF protein was recognized strongly by a monoclonal antibody (mAb104) known to bind the in vivo phosphoepitope shared by SR proteins, indicating that the phosphorylation sites resided in the RS domain. Moreover, the fission yeast U2AF65 homolog, Prp2/Mis11 protein, was phosphorylated more efficiently by Dsk1 than by a **human SR** protein-specific **kinase**, SRPK1. Thus, these in vitro results suggest that Dsk1 is a fission yeast **SR** protein-specific **kinase**, and Prp2/Mis11 is likely an in vivo target for Dsk1. Together with previous genetic data, the studies support the notion that Dsk1 may play a role in coordinating pre-mRNA splicing and the cell division cycle.

L4 ANSWER 53 OF 62 MEDLINE on STN
ACCESSION NUMBER: 1999102948 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9885562
TITLE: Protein phosphorylation plays an essential role in the regulation of alternative splicing and sex determination in Drosophila.
AUTHOR: Du C; McGuffin M E; Dauwalder B; Rabinow L; Mattox W
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha 68198, USA.
SOURCE: Molecular cell, (1998 Dec) 2 (6) 741-50.
Journal code: 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 20020924
Entered Medline: 19990126

AB Alternative mRNA splicing directed by SR proteins and the splicing

regulators TRA and TRA2 is an essential feature of Drosophila sex determination. These factors are highly phosphorylated, but the role of their phosphorylation in vivo is unclear. We show that mutations in the Drosophila LAMMER kinase, Doa, alter sexual differentiation and interact synergistically with tra and tra2 mutations. Doa mutations disrupt sex-specific splicing of doublesex pre-mRNA, a key regulator of sex determination, by affecting the phosphorylation of one or more proteins in the female-specific splicing enhancer complex. Examination of pre-mRNAs regulated similarly to dsx shows that the requirement for Doa is substrate specific. These results demonstrate that a **SR** protein **kinase** plays a specific role in developmentally regulated alternative splicing.

L4 ANSWER 54 OF 62 MEDLINE on STN DUPLICATE 30

ACCESSION NUMBER: 1998139536 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9472028
TITLE: SRPK2: a differentially expressed **SR** protein-specific **kinase** involved in mediating the interaction and localization of pre-mRNA splicing factors in mammalian cells.
AUTHOR: Wang H Y; Lin W; Dyck J A; Yeakley J M; Songyang Z; Cantley L C; Fu X D
CORPORATE SOURCE: Division of Cellular and Molecular Medicine, Department of Medicine, University of California, San Diego, La Jolla, California 92093-0651, USA.
CONTRACT NUMBER: GM52872 (NIGMS)
SOURCE: Journal of cell biology, (1998 Feb 23) 140 (4) 737-50. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U88666
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980326
Last Updated on STN: 20020420
Entered Medline: 19980316

AB Reversible phosphorylation plays an important role in pre-mRNA splicing in mammalian cells. Two kinases, **SR** protein-specific **kinase** (SRPK1) and Clk/Sty, have been shown to phosphorylate the SR family of splicing factors. We report here the cloning and characterization of SRPK2, which is highly related to SRPK1 in sequence, kinase activity, and substrate specificity. Random peptide selection for preferred phosphorylation sites revealed a stringent preference of SRPK2 for SR dipeptides, and the consensus derived may be used to predict potential phosphorylation sites in candidate arginine and serine-rich (RS) domain-containing proteins. Phosphorylation of an SR protein (ASF/SF2) by either SRPK1 or 2 enhanced its interaction with another RS domain-containing protein (U1 70K), and overexpression of either kinase induced specific redistribution of splicing factors in the nucleus. These observations likely reflect the function of the SRPK family of kinases in spliceosome assembly and in mediating the trafficking of splicing factors in mammalian cells. The biochemical and functional similarities between SRPK1 and 2, however, are in contrast to their differences in expression. SRPK1 is highly expressed in pancreas, whereas SRPK2 is highly expressed in brain, although both are coexpressed in other **human** tissues and in many experimental cell lines. Interestingly, SRPK2 also contains a proline-rich sequence at its NH2 terminus, and a recent study showed that this NH2-terminal sequence has the capacity to interact with a WW domain protein in vitro. Together, our studies suggest that different SRPK family members may be uniquely regulated and targeted, thereby contributing to splicing regulation in different tissues, during development, or in response to signaling.

L4 ANSWER 55 OF 62 MEDLINE on STN DUPLICATE 31
ACCESSION NUMBER: 1998113357 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9446799
TITLE: Novel **SR**-protein-specific **kinase**, SRPK2, disassembles nuclear speckles.
AUTHOR: Kuroyanagi N; Onogi H; Wakabayashi T; Hagiwara M
CORPORATE SOURCE: Department of Anatomy, Nagoya University School of Medicine, Japan.
SOURCE: Biochemical and biophysical research communications, (1998 Jan 14) 242 (2) 357-64.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB012290
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980312
Last Updated on STN: 20020420
Entered Medline: 19980227

AB **SR**-protein-specific **kinase** 1 (SRPK1) is first identified as a specific kinase for SR splicing factors. By RT-PCR of a conserved kinase domain, novel **SR**-protein-specific **kinase** clones were isolated from mouse brain. The cloned cDNAs encode a 106 kDa protein (648 amino acids, 92% identical to **human** SRPK1) and a 120 kDa protein (681 amino acids, 58% identical to **human** SRPK1). Therefore, they were designated mSRPK1 and mSRPK2, respectively. Northern blotting revealed the ubiquitous expression of mSRPK1 in all tissues examined and the tissue-specific expression of mSRPK2 in testis, lung, and brain. Both kinases phosphorylated SF2/ASF, a member of SR proteins in vitro and the phosphopeptide mappings were identical, indicating that these kinases phosphorylate the same site of SF2/ASF. Overexpression of mSRPK2 caused disassembly of cotransfected SF2/ASF and endogenous SC35. Our results indicate that SRPK family members may regulate the disassembly of the SR proteins in a tissue-specific manner.

L4 ANSWER 56 OF 62 MEDLINE on STN
ACCESSION NUMBER: 97439710 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9307018
TITLE: Characterization and comparison of four serine- and arginine-rich (**SR**) protein **kinases**.
AUTHOR: Nayler O; Stamm S; Ullrich A
CORPORATE SOURCE: Max-Planck-Institute for Biochemistry, Am Klopferspitz 18A, D-82152 Martinsried, Germany.
SOURCE: Biochemical journal, (1997 Sep 15) 326 (Pt 3) 693-700.
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF033564; GENBANK-AF033565; GENBANK-AF033566
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971024
Last Updated on STN: 20000303
Entered Medline: 19971016

AB Phosphorylated serine- and arginine-rich (SR) proteins are components of the spliceosomal complex, and have been implicated in the control of alternative splicing. Kinases that regulate the phosphorylation and possibly the intranuclear distribution of SR proteins may therefore contribute to changes in choice of splice site. We have cloned three mouse cDNAs with high sequence identity to the family of LAMMER kinases

(i.e. kinases carrying the conserved signature EHLAMMERILG in the catalytic domain). A comparison of their amino acid sequences revealed two related subfamilies with high evolutionary conservation. We have compared the expression patterns of these proteins in mouse tissues and transformed cell lines with that of a previously cloned family member (mCLK1/STY), and detected various transcripts for each gene. This underlines previous findings of alternative splicing of mclk1/STY. Our results suggest that the proportions of products for each gene are regulated independently. We further demonstrate that all variants encode autophosphorylating proteins that can phosphorylate several biochemically purified SR proteins in vitro, leading to hyperphosphorylation of at least one SR protein in vivo. The observed tissue distributions and substrate specificities suggest that these kinases may all be constituents of a network of regulatory mechanisms that enable SR proteins to control RNA splicing.

L4 ANSWER 57 OF 62 MEDLINE on STN
ACCESSION NUMBER: 97346424 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9202841
TITLE: Phosphorylation and regulation of the Ca(2+)-pumping ATPase in cardiac sarcoplasmic reticulum by calcium/calmodulin-dependent protein kinase.
AUTHOR: Narayanan N; Xu A
CORPORATE SOURCE: Department of Physiology, University of Western Ontario London, Canada.
SOURCE: Basic research in cardiology, (1997) 92 Suppl 1 25-35. Ref: 68
Journal code: 0360342. ISSN: 0300-8428.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970908
Last Updated on STN: 19980206
Entered Medline: 19970827

AB In cardiac muscle, a membrane-associated Ca2+/calmodulin-dependent protein kinase (CaM kinase) phosphorylates the Ca(2+)-pumping ATPase in addition to its previously characterized substrates, phospholamban and Ca(2+)-release channel (ryanodine receptor). The phosphorylated amino acid in the Ca(2+)-ATPase has been identified as serine. Posphorylation of the Ca(2+)-ATPase is rapid and is reversible by a membrane-associated protein phosphatase, Ca(2+)-ATPase purified from cardiac **SR** underwent phosphorylation by exogenous CaM **kinase**, and the phosphorylated enzyme displayed twofold greater catalytic activity without alteration in its Ca(2+)-sensitivity. The phosphorylation of the Ca(2+)-ATPase was found to be isoform-specific in that the cardiac and slow-twitch skeletal muscle isoform (SERCA 2), but not the fast-twitch skeletal muscle isoform (SERCA 1), underwent phosphorylation by CaM kinase. Studies using SERCA 1 and SERCA 2 isoforms and their mutants expressed in a heterelogous cell system have resulted in i) confirmation of the isoform specificity of Ca(2+)-ATPase phosphorylation by CaM kinase, ii) identification of Ser38 as the site in SERCA 2 phosphorylated by CaM kinase, and iii) demonstration of phosphorylation-induced increase in Vmax of Ca2+ transport by the SERCA 2 enzyme. These observations suggest that in cardiac and slow-twitch skeletal muscle direct phosphorylation of the SR Ca(2+)-ATPase by the membrane-bound CaM kinase may serve to stimulate Ca2+ sequestration and therefore, the speed of muscle relaxation.

L4 ANSWER 58 OF 62 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:610310 HCAPLUS

DOCUMENT NUMBER: 125:269260
TITLE: Protein serine kinase, SRPK1, phosphorylating SR RNA splicing factors, the gene encoding it
INVENTOR(S): Gui, Jian-fang; Fu, Xiang-dong
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: U.S., 42 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5559019	A	19960924	US 1994-264002	19940622
PRIORITY APPLN. INFO.:			US 1994-264002	19940622

AB A novel serine protein kinase, SRPK1, of about 92 kD and phosphorylating the SR family of splicing factors in a cell-cycle regulated manner is described. Regulation of the kinase, e.g. with pharmaceuticals can be used to regulate the activity and distribution of SR factors and thereby control rates of cell proliferation. Polynucleotide and polypeptide sequences for SRPK1 are provided as well as methods for modulating splicing and alternative splicing of precursor mRNAs.

L4 ANSWER 59 OF 62 MEDLINE on STN DUPLICATE 32
ACCESSION NUMBER: 96196514 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8609994
TITLE: Specific phosphorylation of SR proteins by mammalian DNA topoisomerase I.
AUTHOR: Rossi F; Labourier E; Forne T; Divita G; Derancourt J; Riou J F; Antoine E; Cathala G; Brunel C; Tazi J
CORPORATE SOURCE: Institut de Genetique Moleculaire, Universite de Montpellier II, France.
SOURCE: Nature, (1996 May 2) 381 (6577) 80-2.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19960605
Last Updated on STN: 19980206
Entered Medline: 19960530

AB Several metazoan splicing factors are characterized by ribonucleoprotein (RNP) consensus sequences and arginine-serine repeats (RS domain) which are essential for their function in splicing. These include members of the SR-protein family (SC35, SF2/ASF), the U1 small nuclear (sn) RNP protein (U1-70K) and the U2 snRNP auxiliary factor (U2AF). SR proteins are phosphorylated in vivo and the phosphorylation state of U1-70K's RS domain influences its splicing activity. Here we report the purification of a protein kinase that is specific for SR proteins and show that it is DNA topoisomerase I. This enzyme lacks a canonical ATP-binding motif but binds ATP with a dissociation constant of 50 nM. Camptothecin and derivatives, known to be specific inhibitors of DNA topoisomerase I, strongly inhibit the kinase activity in the presence of DNA and affect the phosphorylation state of SR proteins. Thus, DNA topoisomerase I may well be one of the **SR** protein **kinases** operating in vivo.

L4 ANSWER 60 OF 62 MEDLINE on STN
ACCESSION NUMBER: 95062157 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7526381
TITLE: Purification and characterization of a kinase specific for the serine- and arginine-rich pre-mRNA splicing factors.

AUTHOR: Gui J F; Tronchere H; Chandler S D; Fu X D
CORPORATE SOURCE: Division of Cellular and Molecular Medicine, University of California, San Diego, La Jolla 92093-0651.
CONTRACT NUMBER: GM49369 (NIGMS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1994 Nov 8) 91 (23) 10824-8. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 20020420
Entered Medline: 19941212

AB Members of the SR family of pre-mRNA splicing factors are phosphoproteins that share a phosphoepitope specifically recognized by monoclonal antibody (mAb) 104. Recent studies have indicated that phosphorylation may regulate the activity and the intracellular localization of these splicing factors. Here, we report the purification and kinetic properties of **SR** protein **kinase** 1 (SRPK1), a **kinase** specific for SR family members. We demonstrate that the kinase specifically recognizes the SR domain, which contains serine/arginine repeats. Previous studies have shown that dephosphorylated SR proteins did not react with mAb 104 and migrated faster in SDS gels than SR proteins from mammalian cells. We show that SRPK1 restores both mobility and mAB 104 reactivity to a SR protein SF2/ASF (splicing factor 2/alternative splicing factor) produced in bacteria, suggesting that SRPK1 is responsible for the generation of the mAb 104-specific phosphoepitope in vivo. Finally, we have correlated the effects of mutagenesis in the SR domain of SF2/ASF on splicing with those on phosphorylation of the protein by SRPK1, suggesting that phosphorylation of SR proteins is required for splicing.

L4 ANSWER 61 OF 62 MEDLINE on STN DUPLICATE 33
ACCESSION NUMBER: 94268559 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8208298
TITLE: A serine kinase regulates intracellular localization of splicing factors in the cell cycle.
COMMENT: Comment in: Nature. 1994 Jun 23;369(6482):604. PubMed ID: 8208284
AUTHOR: Gui J F; Lane W S; Fu X D
CORPORATE SOURCE: Division of Cellular and Molecular Medicine, University of California at San Diego 92093-0651.
SOURCE: Nature, (1994 Jun 23) 369 (6482) 678-82. Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M13447; GENBANK-S28282; GENBANK-U09564
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940721
Last Updated on STN: 20020420
Entered Medline: 19940714

AB Small nuclear ribonucleoprotein particles (snRNPs) and non-snRNP splicing factors containing a serine/arginine-rich domain (SR proteins) concentrate in 'speckles' in the nucleus of interphase cells. It is believed that nuclear speckles act as storage sites for splicing factors while splicing occurs on nascent transcripts. Splicing factors redistribute in response to transcription inhibition or viral infection, and nuclear speckles break down and reform as cells progress through mitosis. We have now identified and cloned a kinase, SRPK1, which is regulated by the cell cycle and is specific for **SR** proteins; this **kinase** is related to a

Caenorhabditis elegans kinase and to the fission yeast kinase Dsk1 (reference 7). SRPK1 specifically induces the disassembly of nuclear speckles, and a high level of SRPK1 inhibits splicing in vitro. Our results indicate that SRPK1 may have a central role in the regulatory network for splicing, controlling the intranuclear distribution of splicing factors in interphase cells, and the reorganization of nuclear speckles during mitosis.

L4 ANSWER 62 OF 62 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1994:57210 BIOSIS
DOCUMENT NUMBER: PREV199497070210
TITLE: Clinical features of patients with spontaneous recanalization of the infarct-related artery during evolving myocardial infarction.
AUTHOR(S): Akiyama, Hiroyuki
CORPORATE SOURCE: First Dep. Internal Med., Kinki Univ. Sch. Med., Osaka, Japan
SOURCE: Medical Journal of Kinki University, (1993) Vol. 18, No. 3, pp. 381-401.
CODEN: KDIZDD. ISSN: 0385-8367.
DOCUMENT TYPE: Article
LANGUAGE: Japanese
ENTRY DATE: Entered STN: 9 Feb 1994
Last Updated on STN: 10 Feb 1994

AB Acute myocardial infarction (AMI) with spontaneous recanalization (SR) of infarct-related coronary artery (IRCA) has distinctly different clinical features compared to AMI with occluded arteries. To clarify the pathogenesis of SR, the incidence of SR, anginal episodes prior to the onset of infarction, the character of chest pain at onset, vasodilator response to nitroglycerin in IRCA, and infarct size were studied in 296 patients (pts) with AMI. Pts were divided into three groups, TIMI 0 : 172 with complete occlusion of the artery at the initial coronary angiogram, TIMI 1, 2: 57 with subtotal occlusion and TIMI 3 : 67 with SR. The incidence of SR was 20.3% when coronary angiograms were performed 0-4 hrs after onset, 22.2% at 4-6 hrs, 19.7% at 6-12 hrs, 24.0% at 12-24 hrs and 36.0% more than 24 hrs later. This indicates that the incidence of SR was not dependent on the elapsed time after onset. IRCA may be patent very early after onset and late SR is not more frequent than that occurring within 4 hrs after onset. AMI with SR was characterized by a high incidence of angina before the onset of infarction which was associated with increased coronary vasomotor tone (angina at rest: 28.6%, variable-threshold angina: 38.1%, others : 33.3%). However, AMI with complete occlusion showed only 5.4% of angina at rest and 10.8% of variable-threshold angina. Duration of chest pain was more than 2 hrs in 91.3% of patients with complete occlusion, while 48.6% of patients with SR had chest pain for less than 2 hrs. This would indicate that in SR complete occlusion persisted for a very short time after onset. Intermittent chest pain at onset occurred in 38.8% of SR, suggesting coronary occlusion was intermittent, while only 8.4% of patients with complete occlusion had intermittent pain. Coronary vasodilator response to intracoronary nitroglycerin was measured using the automatic edge detection system. Vasodilatation of the proximal normal adjacent segment to the stenotic lesion of IRCA was only 4.0+-0.6% in complete occlusion, while it was significantly increased (20.7+-2.6%) in SR. This would indicate that IRCA in SR was spastic during the initial coronary angiogram. Infarct size was larger in complete occlusion than in the successfully reperfused group and **SR** as determined by serum creatine **kinase** activity, number of abnormal Q waves, wall motion abnormality on 2-D echocardiogram and left ventriculogram. The infarct size in SR also was smaller than that in the successfully reperfused group, suggesting that IRCA may be patent in SR far earlier

than in the successfully reperfused group. In conclusion, IRCA of SR is either recanalized very early after onset or has an increased coronary vasomotor tone, so-called spasm, at the onset of AMI.

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=> d his

     (FILE 'HOME' ENTERED AT 08:53:58 ON 03 JUN 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 08:54:24 ON 03 JUN 2005
L1       1322846 S KINASE?
L2           551 S SR (5W)L1
L3           166 S HUMAN AND L2
L4            62 DUP REM L3 (104 DUPLICATES REMOVED)

=> s "SRPK"
L5           109 "SRPK"

=> s clon? or express? or recombinant
   4 FILES SEARCHED...
L6       7101940 CLON? OR EXPRESS? OR RECOMBINANT

=> s l5 and l6
L7            54 L5 AND L6

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8            19 DUP REM L7 (35 DUPLICATES REMOVED)

=> d 1-19 ibib ab

L8   ANSWER 1 OF 19  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:224990  HCAPLUS
TITLE:                    Construction of a cDNA expression library of
                          Physarum polycephalum at G2 phase
AUTHOR(S):                Zhang, Jian-hua; Liu, Shi-de; Xing, Miao
CORPORATE SOURCE:         Shenzhen Key Laboratory of Microbial Gene Engineering,
                          College of Life Science, Shenzhen University,
                          Shenzhen, 518060, Peop. Rep. China
SOURCE:                   Shenzhen Daxue Xuebao, Ligongban (2005), 22(1), 50-56
                          CODEN: SDXLEX; ISSN: 1000-2618
PUBLISHER:                Shenzhen Daxue Xuebao, Bianjibu
DOCUMENT TYPE:            Journal
LANGUAGE:                 Chinese
AB   In order to isolate the genes of SC35-like proteins and SRPK
     -like proteins of Physarum polycephalum, a cDNA expression
     library of P. polycephalum at G2 phase was constructed. The titer of the
     primary cDNA library is 1.22 + 106 pfu/mL and of the amplified
     library is 1.12 + 1011 pfu/mL (plaque-forming units, pfu). Almost
     all of the phages in the cDNA library were reconstituted. The size of the
     inserts ranges from 0.5 kb to 2.5 kb. All of the above mentioned have
     answered for the general requirements of a cDNA expression
     library.

L8   ANSWER 2 OF 19     MEDLINE on STN
ACCESSION NUMBER:   2003518851     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 14596595
TITLE:              Novel destabilization of nucleotide binding by the gamma
                    phosphate of ATP in the yeast SR protein kinase Sky1p.
AUTHOR:             Aubol Brandon E; Nolen Brad; Shaffer Jennifer; Ghosh
                    Gourisankar; Adams Joseph A
CORPORATE SOURCE:   Department of Chemistry and Biochemistry, University of
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California, San Diego, La Jolla, California 92093-0506, USA.
CONTRACT NUMBER: GM07752 (NIGMS)
GM68168 (NIGMS)
SOURCE: Biochemistry, (2003 Nov 11) 42 (44) 12813-20.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031105
Last Updated on STN: 20040130
Entered Medline: 20040129

AB SR protein kinases (**SRPKs**) regulate the temporal and cell-specific selection of alternative splice sites. These enzymes are highly unique members of the protein kinase family. **SRPKs** contain a large domain insert (approximately 200 residues) within the kinase core, do not require phosphorylation for regulation, have an extended helix insert near the nucleotide pocket, and possess unusual substrate specificity determinants. The yeast **SRPK**, Sky1p, rapidly phosphorylates its natural substrate Npl3 but binds ATP with a high K(m), suggesting that some of these distinctive structural features may be correlated with nucleotide binding [Aubol et al. (2002) Biochemistry 41, 10002-10009]. To address this issue, the nucleotide binding properties of Sky1p were studied using fluorescence spectroscopy. The affinities of several nucleotides (ATP, ADP, AMP, adenosine, and AMPPNP) to Sky1p and the prototype kinase, cAMP-dependent protein kinase, were compared in the absence and presence of the metal activator, Mg(2+), using a fluorescence-based displacement assay. The data indicate that Sky1p, unlike cAMP-dependent protein kinase, potently destabilizes the gamma phosphate of ATP. This novel finding suggests that rapid phosphoryl transfer may be facilitated by unique mechanisms in both protein kinases.

L8 ANSWER 3 OF 19 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:244778 BIOSIS
DOCUMENT NUMBER: PREV200300244778
TITLE: ICP27 interacts with SRPK1 to mediate HSV splicing inhibition by altering SR protein phosphorylation.
AUTHOR(S): Sciabica, Kathryn S.; Dai, Qian J.; Sandri-Goldin, Rozanne M. [Reprint Author]
CORPORATE SOURCE: Department of Microbiology and Molecular Genetics, University of California, Irvine, CA, 92697, USA
rmsandri@uci.edu
SOURCE: EMBO (European Molecular Biology Organization) Journal, (April 1 2003) Vol. 22, No. 7, pp. 1608-1619. print.
ISSN: 0261-4189 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 21 May 2003
Last Updated on STN: 21 May 2003

AB Infection with some viruses can alter cellular mRNA processing to favor viral gene **expression**. We present evidence that herpes simplex virus 1 (HSV-1) protein ICP27, which contributes to host shut-off by inhibiting pre-mRNA splicing, interacts with essential splicing factors termed SR proteins and affects their phosphorylation. During HSV-1 infection, phosphorylation of several SR proteins was reduced and this correlated with a subnuclear redistribution. Exogenous SR proteins restored splicing in ICP27-inhibited nuclear extracts and SR proteins isolated from HSV-1-infected cells activated splicing in uninfected S100 extracts, indicating that inhibition occurs by a reversible mechanism. Spliceosome assembly was blocked at the pre-spliceosomal complex A stage. Furthermore, we show that ICP27 interacts with SRPK1 and relocalizes it to

the nucleus; moreover, SRPK1 activity was altered in the presence of ICP27 in vitro. We propose that ICP27 modifies SRPK1 activity resulting in hypophosphorylation of SR proteins impairing their ability to function in spliceosome assembly.

L8 ANSWER 4 OF 19 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003148290 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12615332
TITLE: Trypanosoma cruzi TcSRPK, the first protozoan member of the **SRPK** family, is biochemically and functionally conserved with metazoan SR protein-specific kinases.
AUTHOR: Portal Daniel; Lobo Guillermo S; Kadener Sebastian; Prasad Jayendra; Espinosa Joaquin M; Pereira Claudio A; Tang Zhaohua; Lin Ren-Jang; Manley James L; Kornblihtt Alberto R; Flawia Mirtha M; Torres Hector N
CORPORATE SOURCE: Facultad de Ciencias Exactas y Naturales, Instituto de Investigaciones en Ingenieria Genetica y Biologia Molecular, Consejo Nacional de Investigaciones Cientificas y Tecnicas, Universidad de Buenos Aires, Buenos Aires, Argentina.
SOURCE: Molecular and biochemical parasitology, (2003 Mar) 127 (1) 9-21.
Journal code: 8006324. ISSN: 0166-6851.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030401
Last Updated on STN: 20030713
Entered Medline: 20030711
AB A novel SR protein-specific kinase (**SRPK**) from the **SRPK** family was identified for the first time in a protozoan organism. The primary structure of the protein, named TcSRPK, presents a significant degree of identity with other metazoan members of the family. In vitro phosphorylation experiments showed that TcSRPK has the same substrate specificity relative to other **SRPKs**. TcSRPK was able to generate a mAb104-recognized phosphoepitope, a **SRPK** landmark. **Expression** of TcSRPK in different Schizosaccharomyces pombe strains lead to conserved phenotypes, indicating that TcSRPK is a functional homologue of metazoan **SRPKs**. In functional alternative splicing assays in vivo in HeLa cells, TcSRPK enhanced SR protein-dependent inclusion of the EDI exon of the fibronectin minigene. When tested in vitro, it inhibited splicing either on nuclear extracts or on splicing-deficient S100 extracts complemented with ASF/SF2. This inhibition was similar to that observed with human SRPK1. This work constitutes the first report of a member of this family of proteins and the existence of an SR-network in a protozoan organism. The implications in the origins and control of splicing are discussed.

L8 ANSWER 5 OF 19 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
DUPLICATE 2
ACCESSION NUMBER: 2003-09784 BIOTECHDS
TITLE: Identifying candidate p53 pathway-modulating agents useful as therapeutic targets for disorders related with defective p53 function, by screening for agents modulating serine/arginine protein-specific kinase activity;
using antagonist, agonist, antibody, antisense oligonucleotide or phosphothioate morpholino oligonucleotide for drug screening for cancer therapy
AUTHOR: FRIEDMAN L; PLOWMAN G D; BELVIN M; FRANCIS-LANG H; LI D; FUNKE R P
PATENT ASSIGNEE: EXELIXIS INC

PATENT INFO: WO 2002099427 12 Dec'2002
APPLICATION INFO: WO 2002-US17525 3 Jun 2002
PRIORITY INFO: US 2002-357253 15 Feb 2002; US 2001-296076 5 Jun 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-156865 [15]
AB DERWENT ABSTRACT:

NOVELTY - Identifying (M1) candidate p53 pathway-modulating agent comprises screening for agents that modulate the activity of serine/arginine protein-specific kinase, is new.

DETAILED DESCRIPTION - (M1) further comprises: (a) providing an assay system comprising a purified serine/arginine protein-specific kinase (**SRPK**) polypeptide or nucleic acid or its functionally active fragment or derivative; (b) contacting the assay system with a test agent under conditions, where but for the presence of the test agent, the system provides a reference activity; and (c) detecting a test agent-biased activity of the assay system, where a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate p53 pathway-modulating agent. INDEPENDENT CLAIMS are also included for the following: (1) modulating a p53 pathway of a cell comprises contacting a cell defective in p53 function with a candidate modulator that specifically binds to a **SRPK** polypeptide comprising any one of 7 fully defined sequences of 338-1017 amino acids given in the specification, where p53 function is restored; (2) modulating p53 pathway in a mammalian cell comprises contacting the cell with an agent that specifically binds to a **SRPK** polypeptide or nucleic acid; and (3) diagnosing a disease in a patient comprises obtaining a biological sample from the patient, contacting the sample with a probe for **SRPK expression**, comparing the results with a control, and determining whether it indicates a likelihood of a disease.

BIOTECHNOLOGY - Preferred Method: Identifying a candidate p53 pathway-modulating agent, where the assay system comprises cultured cells that **express** the serine/arginine protein-specific kinase (**SRPK**) polypeptide. The cultured cells additionally have defective p53 function. The assay system is selected from the group of an apoptosis assay system, a cell proliferation assay system, an angiogenesis assay system, or a hypoxic induction assay system. The assay system includes: (a) a screening assay comprising a **SRPK** polypeptide and the candidate test agent is a small molecule modulator, where the assay is preferably a kinase assay; (b) a binding assay comprising a **SRPK** polypeptide and the candidate test agent is an antibody; or (c) an **expression** assay comprising a **SRPK** nucleic acid and the candidate test agent is a nucleic acid modulator, which is an antisense oligomer or a phosphothioate morpholino oligomer (PMO). (M1) further comprises administering the identified candidate p53 pathway-modulating agent to a model system comprising cells defective in p53 function, and detecting a phenotypic change in the model system that indicates that the p53 function is restored. The model system is a mouse model system with defective p53 function and additionally comprises: (a) providing a secondary assay system comprising cultured cells or a non-human animal **expressing SRPK**; (b) contacting the secondary assay system with the test agent, or an agent derived from it under conditions, where but for the presence of the test agent or the agent derived from it, the system provides a reference activity; and (c) detecting an agent-biased activity of the second assay system, where a difference between the agent-biased activity and the reference activity of the second assay system confirms the test agent or agent derived from it as a candidate p53 pathway-modulating agent, and where the second assay detects an agent-biased change in the p53 pathway.The secondary assay system comprises cultured cells or a non-human animal, which mis-**expresses** a p53 pathway gene. Modulating a p53 pathway of a cell, where the candidate modulator is administered to a vertebrate animal

pre-determined to have a disease or disorder resulting from a defect in p53 function. The candidate modulator is an antibody or a small molecule. Modulating p53 pathway in a mammalian cell, where the agent is administered to a mammalian animal pre-determined to have a pathology associated with the p53 pathway. The agent is a small molecule modulator, a nucleic acid modulator, or an antibody. Diagnosing a disease in a patient, where the disease is cancer, preferably breast cancer, colon cancer, lung cancer, or ovarian cancer, which has greater than 25% **expression** level.

ACTIVITY - Cytostatic. Test details are described but no results given.

MECHANISM OF ACTION - P53 Agonist; P53 Antagonist.

USE - Invention provides methods for utilizing p53 modifier genes and polypeptides to identify candidate therapeutic agents that can be used in the treatment of disorders associated with defective p53 function. The methods are also useful for modulating p53 pathway in a mammalian cell, or for diagnosing or treating a disease associated with defective p53 function, e.g. cancers such as breast cancer, colon cancer, lung cancer or ovarian cancer. The serine/arginine protein-specific kinase (**SRPK**) polypeptides and nucleic acids are useful for identifying and testing agents that modulate **SRPK** function. The animal models are useful for in vivo assays to test the activity of a candidate p53-modulating agent, or to assess the role of **SRPK** in a p53 pathway process such as apoptosis or cell proliferation.

ADMINISTRATION - Dosage of the antibody is approx. 0.1-10 mg/kg bodyweight.

EXAMPLE - Fluorescently-labeled serine/arginine protein-specific kinase (**SRPK**) peptide/substrate were added to each well of a 96-well microtiter plate, along with a test agent in a test buffer. Changes in fluorescence polarization, determined by using a Fluorolite FPM-2 Fluorescence Polarization Microtiter System, relative to control values indicates the test compound is a candidate modifier of **SRPK** activity.(137 pages)

L8 ANSWER 6 OF 19 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-16041 BIOTECHDS
TITLE: Identifying agents for treatment or prevention of cytomegalovirus infection, comprises contacting test compound with cellular kinase and detecting change in cellular kinase activity;
enzyme inhibition, differential display method and DNA array for disease therapy and drug screening
AUTHOR: SCHUBART D; HABENBERGER P; STEIN-GERLACH M; BEVEC D
PATENT ASSIGNEE: AXXIMA PHARM AG
PATENT INFO: EP 1201765 2 May 2002
APPLICATION INFO: EP 2000-124604 16 Oct 2000
PRIORITY INFO: US 2000-240750 16 Oct 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-373930 [41]
AB DERWENT ABSTRACT:

NOVELTY - Identifying compounds (A) for treating and/or preventing cytomegalovirus (CMV) infection and/or related diseases comprising contacting a test compound with at least one of the cellular kinases RICK, RIP, Nck-Interacting kinase, MKK3 and **SRPK**-2 (undefined) and detecting any change in kinase activity, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) detecting CMV infection and/or related diseases by detecting activity of any of the specified kinases in a patient sample, cells or cell lysates; (2) mono- or poly-**clonal** antibodies (Ab) that bind to any of the specified kinases; (3) preventing and/or treating CMV infection or related diseases, or for regulating production of CMV in an individual or cells, by administering an inhibitor or activator of any

of the specified kinases; (4) oligonucleotides (ON) that bind to RNA or DNA encoding any of the specified kinases; (5) regulating **expression** of any of the specified kinases by administering to an individual, or cells, an inhibitor or activator of transcription of the relevant DNA or translation of the relevant RNA; (6) solid support for detecting CMV infection in an individual or cell comprising at least one immobilized ON able to detect activity of any of the specified kinases; and (7) solid support for screening (A) comprising one or more immobilized ON that encode any of the specified kinases or these kinases themselves.

BIOTECHNOLOGY - Preparation: Differential display methods, using a microarray of more than 1100 signal-transduction cDNAs, was used to compare RNA **expression** profiles in CMV infected and non-infected foreskin fibroblasts, to identify the specified kinases as being upregulated in infected cells. The significance of these kinases was confirmed from the much reduced replication of CMV in cells that **express** a mutant form of RICK or RIP. Preferred Method: In the array used to determine mRNA **expression**, preferred immobilized cDNA oligonucleotides contain 914-2501; 1421-2617; 231-3077; 341-2030 or 1238-2790 base pairs, respectively, regions of RICK, RIP, NIK, MKK3 or **SRPK**-2. Alternatively, determination is at the protein level, e.g. by Western blotting or radioimmunoassay.

ACTIVITY - Virucide. RICK was transiently overexpressed, as a fusion with a hemagglutinin (HA) tag, in human embryonic kidney 293 cells, then immunoprecipitated (anti-HA antibody and protein A-Sepharose). The beads were washed, then tested for kinase activity by incubation in a mixture containing gamma(33P)-adenosine triphosphate and various concentrations of 8-methyl-6-phenyl-2-(pyridin-4-ylamino)-8H-pyrido(2,3-d)pyrimidin-7-one (Aa). After 30 minutes at 30 degrees C, reaction was stopped and phosphorylation determined by electrophoresis and autoradiography. (Aa) has an inhibitory concentration (IC)50 for inhibition of RICK of 500 nM and for inhibition of CMV of 1.4 micro M.

MECHANISM OF ACTION - Modulation of cellular kinases that are specifically upregulated during CMV infection.

USE - (A) are used to treat and/or prevent CMV infections and related diseases. Oligonucleotides that can detect the specified kinases can also be used for diagnosis of infection.

ADMINISTRATION - (A) are administered by inhalation or injection, orally etc. No doses are suggested. (49 pages)

L8 ANSWER 7 OF 19 MEDLINE on STN

ACCESSION NUMBER:	2002385243 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 12134018
TITLE:	Identification of SRPK1 and SRPK2 as the major cellular protein kinases phosphorylating hepatitis B virus core protein.
AUTHOR:	Daub Henrik; Blencke Stephanie; Habenberger Peter; Kurtenbach Alexander; Dennenmoser Julia; Wissing Josef; Ullrich Axel; Cotten Matt
CORPORATE SOURCE:	Axxima Pharmaceuticals AG, 82152 Martinsried, Germany.. daub@axxima.com
SOURCE:	Journal of virology, (2002 Aug) 76 (16) 8124-37. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200208
ENTRY DATE:	Entered STN: 20020723 Last Updated on STN: 20020824 Entered Medline: 20020823

AB Phosphorylation of hepatitis B virus (HBV) core protein has recently been shown to be a prerequisite for pregenomic RNA encapsidation into viral

capsids, but the host cell kinases mediating this essential step of the HBV replication cycle have not been identified. We detected two kinases of 95 and 115 kDa in HuH-7 total cell lysates which interacted specifically with the HBV core protein and phosphorylated its arginine-rich C-terminal domain. The 95-kDa kinase was purified and characterized as SR protein-specific kinase 1 (SRPK1) by mass spectrometry. Based on this finding, the 115-kDa kinase could be identified as the related kinase SRPK2 by immunoblot analysis. In vitro, both **SRPKs** phosphorylated HBV core protein on the same serine residues which are found to be phosphorylated in vivo. Moreover, the major cellular HBV core kinase activity detected in the total cell lysate showed biochemical properties identical to those of SRPK1 and SRPK2, as examined by measuring binding to a panel of chromatography media. We also clearly demonstrate that neither the cyclin-dependent kinases Cdc2 and Cdk2 nor protein kinase C, previously implicated in HBV core protein phosphorylation, can account for the HBV core protein kinase activity. We conclude that both SRPK1 and SRPK2 are most likely the cellular protein kinases mediating HBV core protein phosphorylation during viral infection and therefore represent important host cell targets for therapeutic intervention in HBV infection.

L8 ANSWER 8 OF 19 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002657611 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12417631
TITLE: Human autoimmune sera as molecular probes for the identification of an autoantigen kinase signaling pathway.
AUTHOR: Kamachi Makoto; Le Truc M; Kim Susan J; Geiger Meghan E; Anderson Paul; Utz Paul J
CORPORATE SOURCE: Department of Medicine, Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA 94305, USA.
CONTRACT NUMBER: K08AI01521 (NIAID)
U19-DK61934 (NIDDK)
SOURCE: Journal of experimental medicine, (2002 Nov 4) 196 (9) 1213-25.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021106
Last Updated on STN: 20030110
Entered Medline: 20030109

AB Using human autoimmune sera as molecular probes, we previously described the association of phosphorylated serine/arginine splicing factors (SR splicing factors) with the U1-small nuclear ribonucleoprotein (U1-snRNP) and U3-small nucleolar RNP (snoRNP) in apoptotic cells. SR proteins are highly conserved autoantigens whose activity is tightly regulated by reversible phosphorylation of serine residues by at least eight different SR protein kinase kinases (**SRPKs**), including SRPK1, SRPK2, and the scleroderma autoantigen topoisomerase I. In this report, we demonstrate that only one of the known **SRPKs**, SRPK1, is associated with the U1-snRNP autoantigen complex in healthy and apoptotic cells. SRPK1 is activated early during apoptosis, followed by caspase-mediated proteolytic inactivation at later time points. **SRPKs** are cleaved in vivo after multiple apoptotic stimuli, and cleavage can be inhibited by overexpression of bcl-2 and bcl-x(L), and by exposure to soluble peptide caspase inhibitors. Incubation of **recombinant** caspases with in vitro-translated **SRPKs** demonstrates that SRPK1 and SRPK2 are in vitro substrates for caspases-8 and -9, respectively. In contrast, topoisomerase I is cleaved by downstream caspases (-3 and -6). Since each of these **SRPKs** sits

at a distinct checkpoint in the caspase cascade, **SRPKs** may serve an important role in signaling pathways governing apoptosis, alternative mRNA splicing, SR protein trafficking, RNA stability, and possibly the generation of autoantibodies directed against splicing factors.

L8 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:399415 HCAPLUS
DOCUMENT NUMBER: 139:162417
TITLE: Mediation of the localization of splicing factors in vitro by serine/arginine protein kinase
AUTHOR(S): Lin, Wen; Liu, Zhao; Wang, Huanyou; Fu, Xiangdong
CORPORATE SOURCE: Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, Peop. Rep. China
SOURCE: Zhongguo Zuzhi Huaxue Yu Xibao Huaxue Zazhi (2002), 11(2), 199-201, 240
CODEN: ZZXZFZ; ISSN: 1004-1850
PUBLISHER: Zhongguo Zuzhi Huaxue Yu Xibao Huaxue Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Provide evidence that the serine/arginine protein kinase (**SRPK**) family members mediate the localization of splicing factors in the nucleus. The localizations of both SRPK1 and SRPK2 were determined by peptide tagging or fusing to green fluorescent protein (GFP), and the effect of the **expression** of these kinases on the localization of endogenous splicing factors was examined The results showed that both of these kinases were found in the nucleus and in the cytoplasm, and it was likely that the endogenous kinases were present in both cellular compartments. The splicing factors were concentrated in nuclear speckles in untransfected cells, but diffusely localized in cells **expressing** SRPK1 and SRPK2. The results indicated that **SRPK** family of kinases appears to specifically mediate the redistribution of splicing factors in nucleus.

L8 ANSWER 10 OF 19 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001636611 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11509566
TITLE: **Cloning** and characterization of an alternatively spliced form of SR protein kinase 1 that interacts specifically with scaffold attachment factor-B.
AUTHOR: Nikolakaki E; Kohen R; Hartmann A M; Stamm S; Georgatsou E; Giannakouros T
CORPORATE SOURCE: Laboratory of Biochemistry, School of Chemistry, The Aristotelian University of Thessaloniki, Thessaloniki 54006, Greece.. nikol@ccf.auth.gr
SOURCE: Journal of biological chemistry, (2001 Oct 26) 276 (43) 40175-82. Electronic Publication: 2001-08-16.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ224115; GENBANK-AJ318054
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011107
Last Updated on STN: 20030105
Entered Medline: 20011207
AB Serine/arginine protein kinases have been conserved throughout evolution and are thought to play important roles in the regulation of mRNA processing, nuclear import, germline development, polyamine transport, and ion homeostasis. Human SRPK1, which was first identified as a kinase specific for the SR family of splicing factors, is located on chromosome 6p21.2-p21.3. We report here the **cloning** and characterization

of SRPK1a, which is encoded by an alternatively processed transcript derived from the SRPK1 gene. SRPK1a contains an insertion of 171 amino acids at its NH(2)-terminal domain and is similar to SRPK1 in substrate specificity and subcellular localization. Moreover, both isoforms can induce alternative splicing of human tau exon 10 in transfected cells. Using the yeast two-hybrid assay, we found that the extended NH(2)-terminal domain of SRPK1a interacts with Scaffold Attachment Factor-B, a nuclear scaffold-associated protein. Confirmation of this interaction was provided by in vitro binding assays, as well as by co-immunoprecipitation from 293T cells doubly transfected with SRPK1a and SAF-B. Our studies suggest that different **SRPK** family members are uniquely regulated and targeted and thus the multiple **SRPK** kinases present in higher eukaryotes may perform specialized and differentiable functions.

L8 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:683191 HCAPLUS
DOCUMENT NUMBER: 136:397779
TITLE: Sequencing and analysis of serine/arginine protein-specific kinase
AUTHOR(S): Lin, Wen; Hu, Wensheng; Wang, Huanyou; Fu, Xiangdong
CORPORATE SOURCE: Department of Pediatrics, Xiehe Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, Peop. Rep. China
SOURCE: Tongji Yike Daxue Xuebao (2001), 30(3), 245-247
CODEN: TYDXEP; ISSN: 0258-2090
PUBLISHER: Tongji Yike Daxue
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Serine/arginine protein-specific kinase (SRPK2) was **cloned** to prepare probes. All 8 SRPK1-related EST cDNA **clones** were sequenced by using Erase-a-Base. DNA probes derived from one **clone** were used to screen a human fetal brain cDNA library in the Lamda ZAP II vector. A longest **clone**, 3.744 kb, was sequenced in both strands. The results showed that SRPK2 displayed 77% identity and 90% similarity to SRPK1 over their entire kinase domains. In addition, SRPK2 contained a stretch of proline-rich sequence at the N-terminus. The results showed that SRPK2 might be a new **SRPK** family member with its sequence similar to SRPK1, suggesting both SRPK2 and SRPK1 might have similar enzymic activity and substrate specificity. The N-terminal proline-rich motif might function as a targeting signal to interact with substrates and (or) regulators.

L8 ANSWER 12 OF 19 MEDLINE on STN
ACCESSION NUMBER: 2001148493 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11175909
TITLE: The structure of Sky1p reveals a novel mechanism for constitutive activity.
COMMENT: Comment in: Nat Struct Biol. 2001 Feb;8(2):104-6. PubMed ID: 11175891
AUTHOR: Nolen B; Yun C Y; Wong C F; McCammon J A; Fu X D; Ghosh G
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92130, USA.
SOURCE: Nature structural biology, (2001 Feb) 8 (2) 176-83.
Journal code: 9421566. ISSN: 1072-8368.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1HOW
ENTRY MONTH: 200103

ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20030207
Entered Medline: 20010315

AB Skylp is the only member of the SR protein kinase (**SRPK**) family in Saccharomyces cerevisiae. **SRPKs** are constitutively active kinases that display remarkable substrate specificity and have been implicated in RNA processing. Here we present the three-dimensional structure of a fully active truncated Skylp. Analysis of the structure and structure-based functional studies reveal that the C-terminal tail, an unusual Glu residue located in the P+1 loop, and a unique mechanism for the positioning of helix alpha C act together to render Skylp constitutively active. We have modeled a substrate peptide bound to Skylp. The modeled complex combined with mutagenesis studies illustrate the molecular basis for substrate recognition by this kinase and suggest a mechanism by which **SRPKs** catalyze a sequential phosphorylation reaction of the consecutive RS dipeptide repeats characteristic of mammalian **SRPK** substrates.

L8 ANSWER 13 OF 19 MEDLINE on STN
ACCESSION NUMBER: 2000458663 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10952997
TITLE: Conserved SR protein kinase functions in nuclear import and its action is counteracted by arginine methylation in Saccharomyces cerevisiae.
AUTHOR: Yun C Y; Fu X D
CORPORATE SOURCE: Department of Cellular and Molecular Medicine, University of California at San Diego, La Jolla, California 92093-0651, USA.
SOURCE: Journal of cell biology, (2000 Aug 21) 150 (4) 707-18. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20030207
Entered Medline: 20000928

AB Mammalian serine and arginine-rich (SR) proteins play important roles in both constitutive and regulated splicing, and SR protein-specific kinases (**SRPKs**) are conserved from humans to yeast. Here, we demonstrate a novel function of the single conserved SR protein kinase Skylp in nuclear import in budding yeast. The yeast SR-like protein Npl3p is known to enter the nucleus through a composite nuclear localization signal (NLS) consisting of a repetitive arginine- glycine-glycine (RGG) motif and a nonrepetitive sequence. We found that the latter is the site for phosphorylation by Skylp and that this phosphorylation regulates nuclear import of Npl3p by modulating the interaction of the RGG motif with its nuclear import receptor Mtr10p. The RGG motif is also methylated on arginine residues, but methylation does not affect the Npl3p-Mtr10p interaction in vitro. Remarkably, arginine methylation interferes with Skylp-mediated phosphorylation, thereby indirectly influencing the Npl3p-Mtr10p interaction in vivo and negatively regulating nuclear import of Npl3p. These results suggest that nuclear import of Npl3p is coordinately influenced by methylation and phosphorylation in budding yeast, which may represent conserved components in the dynamic regulation of RNA processing in higher eukaryotic cells.

L8 ANSWER 14 OF 19 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2001137988 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11091073
TITLE: SPK-1, a C. elegans SR protein kinase homologue, is essential for embryogenesis and required for germline

development.
AUTHOR: Kuroyanagi H; Kimura T; Wada K; Hisamoto N; Matsumoto K; Hagiwara M
CORPORATE SOURCE: Molecular Medicine Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, 305-8585, Ibaraki, Japan.
SOURCE: Mechanisms of development, (2000 Dec) 99 (1-2) 51-64. Journal code: 9101218. ISSN: 0925-4773.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010308

AB SR-protein kinases (**SRPKs**) and their substrates, serine/arginine-rich pre-mRNA splicing factors, are key components of splicing machinery and are well conserved across phyla. Despite extensive biochemical investigation, the physiological functions of **SRPKs** remain unclear. In the present study, cDNAs for SPK-1, a C. elegans **SRPK** homologue, and CeSF2, an SPK-1 substrate, were **cloned**. SPK-1 binds directly to and phosphorylates the RS domain of CeSF2 in vitro. Both spk-1 and CeSF2 are predominantly **expressed** in germlines. RNA interference (RNAi) experiments revealed that spk-1 and CeSF2 play an essential role at the embryonic stage of C. elegans. Furthermore, RNAi studies demonstrated that spk-1 is required for germline development in C. elegans. We provide evidence that RNAi, achieved by the soaking of L1 larvae, is beneficial in the study of gene function in post-embryonic germline development.

L8 ANSWER 15 OF 19 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 1999214190 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10196197
TITLE: The subcellular localization of SF2/ASF is regulated by direct interaction with SR protein kinases (**SRPKs**).
AUTHOR: Koizumi J; Okamoto Y; Onogi H; Mayeda A; Krainer A R; Hagiwara M
CORPORATE SOURCE: Department of Functional Genomics, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113, Japan.
CONTRACT NUMBER: CA13106 (NCI)
SOURCE: Journal of biological chemistry, (1999 Apr 16) 274 (16) 11125-31. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 20020420
Entered Medline: 19990517

AB Serine/arginine-rich (SR) proteins play an important role in constitutive and alternative pre-mRNA splicing. The C-terminal arginine-serine domain of these proteins, such as SF2/ASF, mediates protein-protein interactions and is phosphorylated in vivo. Using glutathione S-transferase (GST)-SF2/ASF-affinity chromatography, the SF2/ASF kinase activity was co-purified from HeLa cells with a 95-kDa protein, which was recognized by an anti-SR protein kinase (**SRPK**) 1 monoclonal antibody. **Recombinant** SRPK1 and SRPK2 bound to and phosphorylated GST-SF2/ASF in vitro. Phosphopeptide mapping showed that identical sites

were phosphorylated in the pull-down kinase reaction with HeLa extracts and by **recombinant SRPKs**. Epitope-tagged SF2/ASF transiently **expressed** in COS7 cells co-immunoprecipitated with **SRPKs**. Deletion analysis mapped the phosphorylation sites to a region containing an (Arg-Ser)8 repeat beginning at residue 204, and far-Western analysis showed that the region is required for binding of **SRPKs** to SF2/ASF. Further binding studies showed that **SRPKs** bound unphosphorylated SF2/ASF but did not bind phosphorylated SF2/ASF. **Expression** of an SRPK2 kinase-inactive mutant caused accumulation of SF2/ASF in the cytoplasm. These results suggest that the formation of complexes between SF2/ASF and **SRPKs** , which is influenced by the phosphorylation state of SF2/ASF, may have regulatory roles in the assembly and localization of this splicing factor.

L8 ANSWER 16 OF 19 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1999254059 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10318902
TITLE: Conservation in budding yeast of a kinase specific for SR splicing factors.
AUTHOR: Siebel C W; Feng L; Guthrie C; Fu X D
CORPORATE SOURCE: Department of Biochemistry and Biophysics, University of California, 513 Parnassus Avenue, San Francisco, CA 94143-0448, USA.
CONTRACT NUMBER: 5 T32 CA09270 (NCI)
GM21119 (NIGMS)
GM52872 (NIGMS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1999 May 11) 96 (10) 5440-5. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 20030207
Entered Medline: 19990617

AB SR protein kinases (**SRPKs**) and their substrates, the SR family of serine/arginine-rich pre-mRNA splicing factors, appear to be key regulators of alternative splicing. Although SR proteins have been well characterized through biochemical experiments in metazoans, their functions in vivo are unclear. Because of the strict splice site consensus and near absence of alternative splicing in Saccharomyces cerevisiae, it had been thought that budding yeast would lack an **SRPK** and its substrates. Here, we present structural, biochemical, and cell-biological evidence that directly demonstrates an SR protein kinase, Sky1p, as well as a number of **SRPK** substrates in S. cerevisiae. One of these substrates is Npl3p, an SR-like protein involved in mRNA export. This finding raises the provocative possibility that Sky1p, and by extension metazoan **SRPKs**, regulates mRNA export or the nucleocytoplasmic shuttling of RS domain proteins. The unexpected discovery of an SR protein kinase in budding yeast provides a foundation for genetic dissection of the biological functions of SR proteins and their kinases.

L8 ANSWER 17 OF 19 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:330742 SCISEARCH
THE GENUINE ARTICLE: 188VF
TITLE: Localization of serine kinases, SRPK1 (SFRSK1) and SRPK2 (SFRSK2), specific for the SR family of splicing factors in mouse and human chromosomes
AUTHOR: Wang H Y; Arden K C; Bermingham J R; Viars C S; Lin W;

Boyer A D; Fu X D (Reprint)
CORPORATE SOURCE: UNIV CALIF SAN DIEGO, DIV CELLULAR & MOL MED, 9500 GILMAN DR, LA JOLLA, CA 92093 (Reprint); UNIV CALIF SAN DIEGO, DIV CELLULAR & MOL MED, LA JOLLA, CA 92093; UNIV CALIF SAN DIEGO, LUDWIG INST CANC RES, LA JOLLA, CA 92093; UNIV CALIF SAN DIEGO, HOWARD HUGHES MED INST, DEPT MED, LA JOLLA, CA 92093; UNIV CALIF SAN DIEGO, PROGRAM MOL PATHOL, DEPT PATHOL, LA JOLLA, CA 92093; TONGJI MED UNIV, DEPT PEDIAT, WUHAN 430030, HUBEI, PEOPLES R CHINA; XIE HE HOSP, WUHAN 430030, HUBEI, PEOPLES R CHINA
COUNTRY OF AUTHOR: USA; PEOPLES R CHINA
SOURCE: GENOMICS, (15 APR 1999) Vol. 57, No. 2, pp. 310-315.
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.
ISSN: 0888-7543.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 28
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The serine- and arginine-rich (SR) splicing factors play an important role in both constitutive and alternative pre-mRNA splicing, and the functions of these splicing factors are regulated by phosphorylation. We have previously characterized SRPK1 (SFRSK1) and SRPK2 (SFRSK2), which are highly specific protein kinases for the SR family of splicing factors. Here we report the chromosomal localization of the mouse and human genes for both kinases. SRPK1 probes detected two loci that were mapped to mouse Chromosomes 17 and X using The Jackson Laboratory interspecific backcross DNA panel, and SRPK2 probes identified a single locus on mouse Chromosome 5. Using a somatic cell hybrid mapping panel and by fluorescence in situ hybridization, SRPK1 and SRPK2 were respectively mapped to human chromosomes 6p21.2-p21.3 (a region of conserved synteny to mouse Chromosome 17) and 7q22-q31.1 (a region of conserved synteny to mouse Chromosome 5). In addition, we also found multiple **SRPK**-related sequences on other human chromosomes, one of which appears to correspond to a SRPK2 pseudogene on human chromosome 8. (C) 1999 Academic Press.

L8 ANSWER 18 OF 19 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1998139536 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9472028
TITLE: SRPK2: a differentially **expressed** SR protein-specific kinase involved in mediating the interaction and localization of pre-mRNA splicing factors in mammalian cells.
AUTHOR: Wang H Y; Lin W; Dyck J A; Yeakley J M; Songyang Z; Cantley L C; Fu X D
CORPORATE SOURCE: Division of Cellular and Molecular Medicine, Department of Medicine, University of California, San Diego, La Jolla, California 92093-0651, USA.
CONTRACT NUMBER: GM52872 (NIGMS)
SOURCE: Journal of cell biology, (1998 Feb 23) 140 (4) 737-50.
Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U88666
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980326
Last Updated on STN: 20020420
Entered Medline: 19980316

AB Reversible phosphorylation plays an important role in pre-mRNA splicing in mammalian cells. Two kinases, SR protein-specific kinase (SRPK1) and

Clk/Sty, have been shown to phosphorylate the SR family of splicing factors. We report here the **cloning** and characterization of SRPK2, which is highly related to SRPK1 in sequence, kinase activity, and substrate specificity. Random peptide selection for preferred phosphorylation sites revealed a stringent preference of SRPK2 for SR dipeptides, and the consensus derived may be used to predict potential phosphorylation sites in candidate arginine and serine-rich (RS) domain-containing proteins. Phosphorylation of an SR protein (ASF/SF2) by either SRPK1 or 2 enhanced its interaction with another RS domain-containing protein (U1 70K), and overexpression of either kinase induced specific redistribution of splicing factors in the nucleus. These observations likely reflect the function of the **SRPK** family of kinases in spliceosome assembly and in mediating the trafficking of splicing factors in mammalian cells. The biochemical and functional similarities between SRPK1 and 2, however, are in contrast to their differences in **expression**. SRPK1 is highly **expressed** in pancreas, whereas SRPK2 is highly **expressed** in brain, although both are coexpressed in other human tissues and in many experimental cell lines. Interestingly, SRPK2 also contains a proline-rich sequence at its NH2 terminus, and a recent study showed that this NH2-terminal sequence has the capacity to interact with a WW domain protein in vitro. Together, our studies suggest that different **SRPK** family members may be uniquely regulated and targeted, thereby contributing to splicing regulation in different tissues, during development, or in response to signaling.

L8 ANSWER 19 OF 19 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 1998113357 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9446799
TITLE: Novel SR-protein-specific kinase, SRPK2, disassembles nuclear speckles.
AUTHOR: Kuroyanagi N; Onogi H; Wakabayashi T; Hagiwara M
CORPORATE SOURCE: Department of Anatomy, Nagoya University School of Medicine, Japan.
SOURCE: Biochemical and biophysical research communications, (1998 Jan 14) 242 (2) 357-64.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB012290
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980312
Last Updated on STN: 20020420
Entered Medline: 19980227

AB SR-protein-specific kinase 1 (SRPK1) is first identified as a specific kinase for SR splicing factors. By RT-PCR of a conserved kinase domain, novel SR-protein-specific kinase **clones** were isolated from mouse brain. The **cloned** cDNAs encode a 106 kDa protein (648 amino acids, 92% identical to human SRPK1) and a 120 kDa protein (681 amino acids, 58% identical to human SRPK1). Therefore, they were designated mSRPK1 and mSRPK2, respectively. Northern blotting revealed the ubiquitous **expression** of mSRPK1 in all tissues examined and the tissue-specific **expression** of mSRPK2 in testis, lung, and brain. Both kinases phosphorylated SF2/ASF, a member of SR proteins in vitro and the phosphopeptide mappings were identical, indicating that these kinases phosphorylate the same site of SF2/ASF. Overexpression of mSRPK2 caused disassembly of cotransfected SF2/ASF and endogenous SC35. Our results indicate that **SRPK** family members may regulate the disassembly of the SR proteins in a tissue-specific manner.

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=> d his

     (FILE 'HOME' ENTERED AT 08:53:58 ON 03 JUN 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 08:54:24 ON 03 JUN 2005
L1      1322846 S KINASE?
L2          551 S SR (5W)L1
L3          166 S HUMAN AND L2
L4           62 DUP REM L3 (104 DUPLICATES REMOVED)
L5          109 S "SRPK"
L6      7101940 S CLON? OR EXPRESS? OR RECOMBINANT
L7           54 S L5 AND L6
L8           19 DUP REM L7 (35 DUPLICATES REMOVED)

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E1           42     ABU ZUHRI ALI Z/AU
E2            3     ABU ZURAYK A R/AU
E3            0 --> ABU-THREIDEH J/AU
E4            9     ABUÁ J U/AU
E5            6     ABUAAN M M/AU
E6            3     ABUAAN MOHAMMED M/AU
E7            1     ABUABARA A/AU
E8            8     ABUABARA F/AU
E9           11     ABUABARA J Y/AU
E10           4     ABUABARA K/AU
E11           5     ABUABARA KATRINA/AU
E12           2     ABUABARA M A P/AU

=> e abu  J t/au
E1            1     ABTUSHENKO S S/AU
E2            1     ABTXUSTEGI M M/AU
E3            0 --> ABU  J T/AU
E4            4     ABU A/AU
E5            2     ABU A A/AU
E6            5     ABU A B/AU
E7            1     ABU A M/AU
E8            1     ABU A M Y/AU
E9            6     ABU A O/AU
E10           6     ABU ABDEEN M/AU
E11           1     ABU ABDOU K/AU
E12           3     ABU ABDOU KHALIL/AU

=> e gong f/au
E1            1     GONG ENXIANG/AU
E2            7     GONG EUN YEUNG/AU
E3          238 --> GONG F/AU
E4           36     GONG F C/AU
E5           23     GONG F F/AU
E6            8     GONG F H/AU
E7            3     GONG F J/AU
E8            1     GONG F K/AU
E9           51     GONG F L/AU
E10           2     GONG F M/AU
E11           8     GONG F Q/AU
E12           1     GONG F R/AU

=> s e3
L9          238 "GONG F"/AU

=> e ketchum k a/au
E1            1     KETCHUM JR R L/AU
E2           34     KETCHUM K/AU
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E3          235 --> KETCHUM K A/AU
E4            1     KETCHUM K J/AU
E5           34     KETCHUM K L/AU
E6           22     KETCHUM KAREN/AU
E7          188     KETCHUM KAREN A/AU
E8            1     KETCHUM KAREN ANN/AU
E9            2     KETCHUM KATHY/AU
E10           2     KETCHUM KATHY L/AU
E11           4     KETCHUM KEVIN/AU
E12           3     KETCHUM KEVIN L/AU

=> s e3-e7
L10         480 ("KETCHUM K A"/AU OR "KETCHUM K J"/AU OR "KETCHUM K L"/AU OR
                "KETCHUM KAREN"/AU OR "KETCHUM KAREN A"/AU)

=> e difrancesco v/au
E1            1     DIFRANCESCO U/AU
E2            1     DIFRANCESCO U M/AU
E3          100 --> DIFRANCESCO V/AU
E4           17     DIFRANCESCO VALENTINA/AU
E5            1     DIFRANCESCOL/AU
E6            1     DIFRANCESO D/AU
E7            2     DIFRANCESO L/AU
E8            1     DIFRANCESO R/AU
E9            1     DIFRANCESO ROBIN/AU
E10           1     DIFRANCESSO L/AU
E11           6     DIFRANCIA C/AU
E12           4     DIFRANCIA CELENE/AU

=> s e3
L11         100 "DIFRANCESCO V"/AU

=> e beasley e m/au
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E2            6     BEASLEY E L/AU
E3          327 --> BEASLEY E M/AU
E4            7     BEASLEY E O/AU
E5            1     BEASLEY E S G/AU
E6            2     BEASLEY E T/AU
E7            4     BEASLEY E W/AU
E8            2     BEASLEY E W 3RD/AU
E9            2     BEASLEY E W III/AU
E10           1     BEASLEY E W JR/AU
E11           1     BEASLEY EDWARD E/AU
E12           1     BEASLEY EDWARD EVANS/AU

=> s e3
L12         327 "BEASLEY E M"/AU

=> d his

     (FILE 'HOME' ENTERED AT 08:53:58 ON 03 JUN 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 08:54:24 ON 03 JUN 2005
L1       1322846 S KINASE?
L2           551 S SR (5W)L1
L3           166 S HUMAN AND L2
L4            62 DUP REM L3 (104 DUPLICATES REMOVED)
L5           109 S "SRPK"
L6       7101940 S CLON? OR EXPRESS? OR RECOMBINANT
L7            54 S L5 AND L6
L8            19 DUP REM L7 (35 DUPLICATES REMOVED)
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                E ABU-THREIDEH J/AU
                E ABU  J T/AU
                E GONG F/AU
L9          238 S E3
                E KETCHUM K A/AU
L10         480 S E3-E7
                E DIFRANCESCO V/AU
L11         100 S E3
                E BEASLEY E M/AU
L12         327 S E3

=> s l8 or l9 or l10 or l11 or l12
L13         993 L8 OR L9 OR L10 OR L11 OR L12

=> s l3 or l5
L14         227 L3 OR L5

=> s l13 and l14
L15          21 L13 AND L14

=> d 1-21 ibib ab

L15  ANSWER 1 OF 21     MEDLINE on STN
ACCESSION NUMBER:   2003518851     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 14596595
TITLE:              Novel destabilization of nucleotide binding by the gamma
                    phosphate of ATP in the yeast SR protein kinase Sky1p.
AUTHOR:             Aubol Brandon E; Nolen Brad; Shaffer Jennifer; Ghosh
                    Gourisankar; Adams Joseph A
CORPORATE SOURCE:   Department of Chemistry and Biochemistry, University of
                    California, San Diego, La Jolla, California 92093-0506,
                    USA.
CONTRACT NUMBER:    GM07752 (NIGMS)
     GM68168 (NIGMS)
SOURCE:             Biochemistry, (2003 Nov 11) 42 (44) 12813-20.
                    Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200401
ENTRY DATE:         Entered STN: 20031105
                    Last Updated on STN: 20040130
                    Entered Medline: 20040129
AB   SR protein kinases (SRPKs) regulate the temporal and
     cell-specific selection of alternative splice sites.  These enzymes are
     highly unique members of the protein kinase family.  SRPKs
     contain a large domain insert (approximately 200 residues) within the
     kinase core, do not require phosphorylation for regulation, have an
     extended helix insert near the nucleotide pocket, and possess unusual
     substrate specificity determinants.  The yeast SRPK, Sky1p,
     rapidly phosphorylates its natural substrate Npl3 but binds ATP with a
     high K(m), suggesting that some of these distinctive structural features
     may be correlated with nucleotide binding [Aubol et al. (2002)
     Biochemistry 41, 10002-10009].  To address this issue, the nucleotide
     binding properties of Sky1p were studied using fluorescence spectroscopy.
     The affinities of several nucleotides (ATP, ADP, AMP, adenosine, and
     AMPPNP) to Sky1p and the prototype kinase, cAMP-dependent protein kinase,
     were compared in the absence and presence of the metal activator, Mg(2+),
     using a fluorescence-based displacement assay.  The data indicate that
     Sky1p, unlike cAMP-dependent protein kinase, potently destabilizes the
     gamma phosphate of ATP.  This novel finding suggests that rapid phosphoryl
     transfer may be facilitated by unique mechanisms in both protein kinases.
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L15 ANSWER 2 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2003148290 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12615332
TITLE: Trypanosoma cruzi TcSRPK, the first protozoan member of the **SRPK** family, is biochemically and functionally conserved with metazoan **SR** protein-specific **kinases**.
AUTHOR: Portal Daniel; Lobo Guillermo S; Kadener Sebastian; Prasad Jayendra; Espinosa Joaquin M; Pereira Claudio A; Tang Zhaohua; Lin Ren-Jang; Manley James L; Kornblihtt Alberto R; Flawia Mirtha M; Torres Hector N
CORPORATE SOURCE: Facultad de Ciencias Exactas y Naturales, Instituto de Investigaciones en Ingenieria Genetica y Biologia Molecular, Consejo Nacional de Investigaciones Cientificas y Tecnicas, Universidad de Buenos Aires, Buenos Aires, Argentina.
SOURCE: Molecular and biochemical parasitology, (2003 Mar) 127 (1) 9-21.
Journal code: 8006324. ISSN: 0166-6851.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030401
Last Updated on STN: 20030713
Entered Medline: 20030711

AB A novel **SR** protein-specific **kinase** (**SRPK**) from the **SRPK** family was identified for the first time in a protozoan organism. The primary structure of the protein, named TcSRPK, presents a significant degree of identity with other metazoan members of the family. In vitro phosphorylation experiments showed that TcSRPK has the same substrate specificity relative to other **SRPKs**. TcSRPK was able to generate a mAb104-recognized phosphoepitope, a **SRPK** landmark. **Expression** of TcSRPK in different Schizosaccharomyces pombe strains lead to conserved phenotypes, indicating that TcSRPK is a functional homologue of metazoan **SRPKs**. In functional alternative splicing assays in vivo in HeLa cells, TcSRPK enhanced SR protein-dependent inclusion of the EDI exon of the fibronectin minigene. When tested in vitro, it inhibited splicing either on nuclear extracts or on splicing-deficient S100 extracts complemented with ASF/SF2. This inhibition was similar to that observed with **human** SRPK1. This work constitutes the first report of a member of this family of proteins and the existence of an SR-network in a protozoan organism. The implications in the origins and control of splicing are discussed.

L15 ANSWER 3 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2002657611 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12417631
TITLE: **Human** autoimmune sera as molecular probes for the identification of an autoantigen kinase signaling pathway.
AUTHOR: Kamachi Makoto; Le Truc M; Kim Susan J; Geiger Meghan E; Anderson Paul; Utz Paul J
CORPORATE SOURCE: Department of Medicine, Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA 94305, USA.
CONTRACT NUMBER: K08AI01521 (NIAID)
U19-DK61934 (NIDDK)
SOURCE: Journal of experimental medicine, (2002 Nov 4) 196 (9) 1213-25.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021106
Last Updated on STN: 20030110
Entered Medline: 20030109

AB Using **human** autoimmune sera as molecular probes, we previously described the association of phosphorylated serine/arginine splicing factors (SR splicing factors) with the U1-small nuclear ribonucleoprotein (U1-snRNP) and U3-small nucleolar RNP (snoRNP) in apoptotic cells. SR proteins are highly conserved autoantigens whose activity is tightly regulated by reversible phosphorylation of serine residues by at least eight different **SR** protein **kinase kinases** (**SRPKs**), including SRPK1, SRPK2, and the scleroderma autoantigen topoisomerase I. In this report, we demonstrate that only one of the known **SRPKs**, SRPK1, is associated with the U1-snRNP autoantigen complex in healthy and apoptotic cells. SRPK1 is activated early during apoptosis, followed by caspase-mediated proteolytic inactivation at later time points. **SRPKs** are cleaved in vivo after multiple apoptotic stimuli, and cleavage can be inhibited by overexpression of bcl-2 and bcl-x(L), and by exposure to soluble peptide caspase inhibitors. Incubation of **recombinant** caspases with in vitro-translated **SRPKs** demonstrates that SRPK1 and SRPK2 are in vitro substrates for caspases-8 and -9, respectively. In contrast, topoisomerase I is cleaved by downstream caspases (-3 and -6). Since each of these **SRPKs** sits at a distinct checkpoint in the caspase cascade, **SRPKs** may serve an important role in signaling pathways governing apoptosis, alternative mRNA splicing, SR protein trafficking, RNA stability, and possibly the generation of autoantibodies directed against splicing factors.

L15 ANSWER 4 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2002385243 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12134018
TITLE: Identification of SRPK1 and SRPK2 as the major cellular protein kinases phosphorylating hepatitis B virus core protein.
AUTHOR: Daub Henrik; Blencke Stephanie; Habenberger Peter; Kurtenbach Alexander; Dennenmoser Julia; Wissing Josef; Ullrich Axel; Cotten Matt
CORPORATE SOURCE: Axxima Pharmaceuticals AG, 82152 Martinsried, Germany.. daub@axxima.com
SOURCE: Journal of virology, (2002 Aug) 76 (16) 8124-37. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020723
Last Updated on STN: 20020824
Entered Medline: 20020823

AB Phosphorylation of hepatitis B virus (HBV) core protein has recently been shown to be a prerequisite for pregenomic RNA encapsidation into viral capsids, but the host cell kinases mediating this essential step of the HBV replication cycle have not been identified. We detected two kinases of 95 and 115 kDa in HuH-7 total cell lysates which interacted specifically with the HBV core protein and phosphorylated its arginine-rich C-terminal domain. The 95-kDa kinase was purified and characterized as **SR** protein-specific **kinase** 1 (SRPK1) by mass spectrometry. Based on this finding, the 115-kDa kinase could be identified as the related kinase SRPK2 by immunoblot analysis. In vitro,

both **SRPKs** phosphorylated HBV core protein on the same serine residues which are found to be phosphorylated in vivo. Moreover, the major cellular HBV core kinase activity detected in the total cell lysate showed biochemical properties identical to those of SRPK1 and SRPK2, as examined by measuring binding to a panel of chromatography media. We also clearly demonstrate that neither the cyclin-dependent kinases Cdc2 and Cdk2 nor protein kinase C, previously implicated in HBV core protein phosphorylation, can account for the HBV core protein kinase activity. We conclude that both SRPK1 and SRPK2 are most likely the cellular protein kinases mediating HBV core protein phosphorylation during viral infection and therefore represent important host cell targets for therapeutic intervention in HBV infection.

L15 ANSWER 5 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2001636611 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11509566
TITLE: **Cloning** and characterization of an alternatively spliced form of **SR** protein **kinase** 1 that interacts specifically with scaffold attachment factor-B.
AUTHOR: Nikolakaki E; Kohen R; Hartmann A M; Stamm S; Georgatsou E; Giannakouros T
CORPORATE SOURCE: Laboratory of Biochemistry, School of Chemistry, The Aristotelian University of Thessaloniki, Thessaloniki 54006, Greece.. nikol@ccf.auth.gr
SOURCE: Journal of biological chemistry, (2001 Oct 26) 276 (43) 40175-82. Electronic Publication: 2001-08-16. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ224115; GENBANK-AJ318054
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011107
Last Updated on STN: 20030105
Entered Medline: 20011207

AB Serine/arginine protein kinases have been conserved throughout evolution and are thought to play important roles in the regulation of mRNA processing, nuclear import, germline development, polyamine transport, and ion homeostasis. **Human** SRPK1, which was first identified as a kinase specific for the SR family of splicing factors, is located on chromosome 6p21.2-p21.3. We report here the **cloning** and characterization of SRPK1a, which is encoded by an alternatively processed transcript derived from the SRPK1 gene. SRPK1a contains an insertion of 171 amino acids at its NH(2)-terminal domain and is similar to SRPK1 in substrate specificity and subcellular localization. Moreover, both isoforms can induce alternative splicing of **human** tau exon 10 in transfected cells. Using the yeast two-hybrid assay, we found that the extended NH(2)-terminal domain of SRPK1a interacts with Scaffold Attachment Factor-B, a nuclear scaffold-associated protein. Confirmation of this interaction was provided by in vitro binding assays, as well as by co-immunoprecipitation from 293T cells doubly transfected with SRPK1a and SAF-B. Our studies suggest that different **SRPK** family members are uniquely regulated and targeted and thus the multiple **SRPK** kinases present in higher eukaryotes may perform specialized and differentiable functions.

L15 ANSWER 6 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2001148493 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11175909
TITLE: The structure of Skylp reveals a novel mechanism for constitutive activity.

COMMENT: Comment in: Nat Struct Biol. 2001 Feb;8(2):104-6. PubMed ID: 11175891
AUTHOR: Nolen B; Yun C Y; Wong C F; McCammon J A; Fu X D; Ghosh G
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92130, USA.
SOURCE: Nature structural biology, (2001 Feb) 8 (2) 176-83. Journal code: 9421566. ISSN: 1072-8368.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1HOW
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20030207
Entered Medline: 20010315

AB Sky1p is the only member of the SR protein kinase (**SRPK**) family in Saccharomyces cerevisiae. **SRPKs** are constitutively active kinases that display remarkable substrate specificity and have been implicated in RNA processing. Here we present the three-dimensional structure of a fully active truncated Sky1p. Analysis of the structure and structure-based functional studies reveal that the C-terminal tail, an unusual Glu residue located in the P+1 loop, and a unique mechanism for the positioning of helix alpha C act together to render Sky1p constitutively active. We have modeled a substrate peptide bound to Sky1p. The modeled complex combined with mutagenesis studies illustrate the molecular basis for substrate recognition by this kinase and suggest a mechanism by which **SRPKs** catalyze a sequential phosphorylation reaction of the consecutive RS dipeptide repeats characteristic of mammalian **SRPK** substrates.

L15 ANSWER 7 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2001137988 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11091073
TITLE: SPK-1, a C. elegans SR protein kinase homologue, is essential for embryogenesis and required for germline development.
AUTHOR: Kuroyanagi H; Kimura T; Wada K; Hisamoto N; Matsumoto K; Hagiwara M
CORPORATE SOURCE: Molecular Medicine Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, 305-8585, Ibaraki, Japan.
SOURCE: Mechanisms of development, (2000 Dec) 99 (1-2) 51-64. Journal code: 9101218. ISSN: 0925-4773.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010308

AB SR-protein kinases (**SRPKs**) and their substrates, serine/arginine-rich pre-mRNA splicing factors, are key components of splicing machinery and are well conserved across phyla. Despite extensive biochemical investigation, the physiological functions of **SRPKs** remain unclear. In the present study, cDNAs for SPK-1, a C. elegans **SRPK** homologue, and CeSF2, an SPK-1 substrate, were **cloned** . SPK-1 binds directly to and phosphorylates the RS domain of CeSF2 in vitro. Both spk-1 and CeSF2 are predominantly **expressed** in germlines. RNA interference (RNAi) experiments revealed that spk-1 and CeSF2 play an essential role at the embryonic stage of C. elegans.

Furthermore, RNAi studies demonstrated that spk-1 is required for germline development in C. elegans. We provide evidence that RNAi, achieved by the soaking of L1 larvae, is beneficial in the study of gene function in post-embryonic germline development.

L15 ANSWER 8 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2000458663 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10952997
TITLE: Conserved **SR** protein **kinase** functions in nuclear import and its action is counteracted by arginine methylation in Saccharomyces cerevisiae.
AUTHOR: Yun C Y; Fu X D
CORPORATE SOURCE: Department of Cellular and Molecular Medicine, University of California at San Diego, La Jolla, California 92093-0651, USA.
SOURCE: Journal of cell biology, (2000 Aug 21) 150 (4) 707-18. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20030207
Entered Medline: 20000928

AB Mammalian serine and arginine-rich (SR) proteins play important roles in both constitutive and regulated splicing, and **SR** protein-specific **kinases** (**SRPKs**) are conserved from **humans** to yeast. Here, we demonstrate a novel function of the single conserved **SR** protein **kinase** Sky1p in nuclear import in budding yeast. The yeast SR-like protein Npl3p is known to enter the nucleus through a composite nuclear localization signal (NLS) consisting of a repetitive arginine- glycine-glycine (RGG) motif and a nonrepetitive sequence. We found that the latter is the site for phosphorylation by Sky1p and that this phosphorylation regulates nuclear import of Npl3p by modulating the interaction of the RGG motif with its nuclear import receptor Mtr10p. The RGG motif is also methylated on arginine residues, but methylation does not affect the Npl3p-Mtr10p interaction in vitro. Remarkably, arginine methylation interferes with Sky1p-mediated phosphorylation, thereby indirectly influencing the Npl3p-Mtr10p interaction in vivo and negatively regulating nuclear import of Npl3p. These results suggest that nuclear import of Npl3p is coordinately influenced by methylation and phosphorylation in budding yeast, which may represent conserved components in the dynamic regulation of RNA processing in higher eukaryotic cells.

L15 ANSWER 9 OF 21 MEDLINE on STN
ACCESSION NUMBER: 1999254059 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10318902
TITLE: Conservation in budding yeast of a kinase specific for SR splicing factors.
AUTHOR: Siebel C W; Feng L; Guthrie C; Fu X D
CORPORATE SOURCE: Department of Biochemistry and Biophysics, University of California, 513 Parnassus Avenue, San Francisco, CA 94143-0448, USA.
CONTRACT NUMBER: 5 T32 CA09270 (NCI)
GM21119 (NIGMS)
GM52872 (NIGMS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1999 May 11) 96 (10) 5440-5. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 20030207
Entered Medline: 19990617

AB SR protein kinases (**SRPKs**) and their substrates, the SR family of serine/arginine-rich pre-mRNA splicing factors, appear to be key regulators of alternative splicing. Although SR proteins have been well characterized through biochemical experiments in metazoans, their functions in vivo are unclear. Because of the strict splice site consensus and near absence of alternative splicing in Saccharomyces cerevisiae, it had been thought that budding yeast would lack an **SRPK** and its substrates. Here, we present structural, biochemical, and cell-biological evidence that directly demonstrates an SR protein kinase, Sky1p, as well as a number of **SRPK** substrates in S. cerevisiae. One of these substrates is Npl3p, an SR-like protein involved in mRNA export. This finding raises the provocative possibility that Sky1p, and by extension metazoan **SRPKs**, regulates mRNA export or the nucleocytoplasmic shuttling of RS domain proteins. The unexpected discovery of an SR protein kinase in budding yeast provides a foundation for genetic dissection of the biological functions of SR proteins and their kinases.

L15 ANSWER 10 OF 21 MEDLINE on STN
ACCESSION NUMBER: 1999214190 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10196197
TITLE: The subcellular localization of SF2/ASF is regulated by direct interaction with **SR** protein **kinases** (**SRPKs**).
AUTHOR: Koizumi J; Okamoto Y; Onogi H; Mayeda A; Krainer A R; Hagiwara M
CORPORATE SOURCE: Department of Functional Genomics, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113, Japan.
CONTRACT NUMBER: CA13106 (NCI)
SOURCE: Journal of biological chemistry, (1999 Apr 16) 274 (16) 11125-31.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 20020420
Entered Medline: 19990517

AB Serine/arginine-rich (SR) proteins play an important role in constitutive and alternative pre-mRNA splicing. The C-terminal arginine-serine domain of these proteins, such as SF2/ASF, mediates protein-protein interactions and is phosphorylated in vivo. Using glutathione S-transferase (GST)-SF2/ASF-affinity chromatography, the SF2/ASF kinase activity was co-purified from HeLa cells with a 95-kDa protein, which was recognized by an anti-**SR** protein **kinase** (**SRPK**) 1 monoclonal antibody. **Recombinant** SRPK1 and SRPK2 bound to and phosphorylated GST-SF2/ASF in vitro. Phosphopeptide mapping showed that identical sites were phosphorylated in the pull-down kinase reaction with HeLa extracts and by **recombinant SRPKs**. Epitope-tagged SF2/ASF transiently **expressed** in COS7 cells co-immunoprecipitated with **SRPKs**. Deletion analysis mapped the phosphorylation sites to a region containing an (Arg-Ser)8 repeat beginning at residue 204, and far-Western analysis showed that the region is required for binding of **SRPKs** to SF2/ASF. Further binding

studies showed that **SRPKs** bound unphosphorylated SF2/ASF but did not bind phosphorylated SF2/ASF. **Expression** of an SRPK2 kinase-inactive mutant caused accumulation of SF2/ASF in the cytoplasm. These results suggest that the formation of complexes between SF2/ASF and **SRPKs**, which is influenced by the phosphorylation state of SF2/ASF, may have regulatory roles in the assembly and localization of this splicing factor.

L15 ANSWER 11 OF 21 MEDLINE on STN
ACCESSION NUMBER: 1998139536 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9472028
TITLE: SRPK2: a differentially **expressed SR** protein-specific **kinase** involved in mediating the interaction and localization of pre-mRNA splicing factors in mammalian cells.
AUTHOR: Wang H Y; Lin W; Dyck J A; Yeakley J M; Songyang Z; Cantley L C; Fu X D
CORPORATE SOURCE: Division of Cellular and Molecular Medicine, Department of Medicine, University of California, San Diego, La Jolla, California 92093-0651, USA.
CONTRACT NUMBER: GM52872 (NIGMS)
SOURCE: Journal of cell biology, (1998 Feb 23) 140 (4) 737-50. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U88666
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980326
Last Updated on STN: 20020420
Entered Medline: 19980316

AB Reversible phosphorylation plays an important role in pre-mRNA splicing in mammalian cells. Two kinases, **SR** protein-specific **kinase** (SRPK1) and Clk/Sty, have been shown to phosphorylate the SR family of splicing factors. We report here the **cloning** and characterization of SRPK2, which is highly related to SRPK1 in sequence, kinase activity, and substrate specificity. Random peptide selection for preferred phosphorylation sites revealed a stringent preference of SRPK2 for SR dipeptides, and the consensus derived may be used to predict potential phosphorylation sites in candidate arginine and serine-rich (RS) domain-containing proteins. Phosphorylation of an SR protein (ASF/SF2) by either SRPK1 or 2 enhanced its interaction with another RS domain-containing protein (U1 70K), and overexpression of either kinase induced specific redistribution of splicing factors in the nucleus. These observations likely reflect the function of the **SRPK** family of kinases in spliceosome assembly and in mediating the trafficking of splicing factors in mammalian cells. The biochemical and functional similarities between SRPK1 and 2, however, are in contrast to their differences in **expression**. SRPK1 is highly **expressed** in pancreas, whereas SRPK2 is highly **expressed** in brain, although both are coexpressed in other **human** tissues and in many experimental cell lines. Interestingly, SRPK2 also contains a proline-rich sequence at its NH2 terminus, and a recent study showed that this NH2-terminal sequence has the capacity to interact with a WW domain protein in vitro. Together, our studies suggest that different **SRPK** family members may be uniquely regulated and targeted, thereby contributing to splicing regulation in different tissues, during development, or in response to signaling.

L15 ANSWER 12 OF 21 MEDLINE on STN
ACCESSION NUMBER: 1998113357 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9446799

TITLE: Novel **SR**-protein-specific **kinase**, SRPK2, disassembles nuclear speckles.
AUTHOR: Kuroyanagi N; Onogi H; Wakabayashi T; Hagiwara M
CORPORATE SOURCE: Department of Anatomy, Nagoya University School of Medicine, Japan.
SOURCE: Biochemical and biophysical research communications, (1998 Jan 14) 242 (2) 357-64.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB012290
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980312
Last Updated on STN: 20020420
Entered Medline: 19980227

AB **SR**-protein-specific **kinase** 1 (SRPK1) is first identified as a specific kinase for SR splicing factors. By RT-PCR of a conserved kinase domain, novel **SR**-protein-specific **kinase clones** were isolated from mouse brain. The **cloned** cDNAs encode a 106 kDa protein (648 amino acids, 92% identical to **human** SRPK1) and a 120 kDa protein (681 amino acids, 58% identical to **human** SRPK1). Therefore, they were designated mSRPK1 and mSRPK2, respectively. Northern blotting revealed the ubiquitous **expression** of mSRPK1 in all tissues examined and the tissue-specific **expression** of mSRPK2 in testis, lung, and brain. Both kinases phosphorylated SF2/ASF, a member of SR proteins in vitro and the phosphopeptide mappings were identical, indicating that these kinases phosphorylate the same site of SF2/ASF. Overexpression of mSRPK2 caused disassembly of cotransfected SF2/ASF and endogenous SC35. Our results indicate that **SRPK** family members may regulate the disassembly of the SR proteins in a tissue-specific manner.

L15 ANSWER 13 OF 21 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:244778 BIOSIS
DOCUMENT NUMBER: PREV200300244778
TITLE: ICP27 interacts with SRPK1 to mediate HSV splicing inhibition by altering SR protein phosphorylation.
AUTHOR(S): Sciabica, Kathryn S.; Dai, Qian J.; Sandri-Goldin, Rozanne M. [Reprint Author]
CORPORATE SOURCE: Department of Microbiology and Molecular Genetics, University of California, Irvine, CA, 92697, USA
rmsandri@uci.edu
SOURCE: EMBO (European Molecular Biology Organization) Journal, (April 1 2003) Vol. 22, No. 7, pp. 1608-1619. print.
ISSN: 0261-4189 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 21 May 2003
Last Updated on STN: 21 May 2003

AB Infection with some viruses can alter cellular mRNA processing to favor viral gene **expression**. We present evidence that herpes simplex virus 1 (HSV-1) protein ICP27, which contributes to host shut-off by inhibiting pre-mRNA splicing, interacts with essential splicing factors termed SR proteins and affects their phosphorylation. During HSV-1 infection, phosphorylation of several SR proteins was reduced and this correlated with a subnuclear redistribution. Exogenous SR proteins restored splicing in ICP27-inhibited nuclear extracts and SR proteins isolated from HSV-1-infected cells activated splicing in uninfected S100 extracts, indicating that inhibition occurs by a reversible mechanism. Spliceosome assembly was blocked at the pre-spliceosomal complex A stage.

Furthermore, we show that ICP27 interacts with SRPK1 and relocalizes it to the nucleus; moreover, SRPK1 activity was altered in the presence of ICP27 in vitro. We propose that ICP27 modifies SRPK1 activity resulting in hypophosphorylation of SR proteins impairing their ability to function in spliceosome assembly.

L15 ANSWER 14 OF 21 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-09784 BIOTECHDS
TITLE: Identifying candidate p53 pathway-modulating agents useful as therapeutic targets for disorders related with defective p53 function, by screening for agents modulating serine/arginine protein-specific kinase activity;
using antagonist, agonist, antibody, antisense oligonucleotide or phosphothioate morpholino oligonucleotide for drug screening for cancer therapy
AUTHOR: FRIEDMAN L; PLOWMAN G D; BELVIN M; FRANCIS-LANG H; LI D; FUNKE R P
PATENT ASSIGNEE: EXELIXIS INC
PATENT INFO: WO 2002099427 12 Dec 2002
APPLICATION INFO: WO 2002-US17525 3 Jun 2002
PRIORITY INFO: US 2002-357253 15 Feb 2002; US 2001-296076 5 Jun 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-156865 [15]
AB DERWENT ABSTRACT:
NOVELTY - Identifying (M1) candidate p53 pathway-modulating agent comprises screening for agents that modulate the activity of serine/arginine protein-specific kinase, is new.

DETAILED DESCRIPTION - (M1) further comprises: (a) providing an assay system comprising a purified serine/arginine protein-specific kinase (**SRPK**) polypeptide or nucleic acid or its functionally active fragment or derivative; (b) contacting the assay system with a test agent under conditions, where but for the presence of the test agent, the system provides a reference activity; and (c) detecting a test agent-biased activity of the assay system, where a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate p53 pathway-modulating agent. INDEPENDENT CLAIMS are also included for the following: (1) modulating a p53 pathway of a cell comprises contacting a cell defective in p53 function with a candidate modulator that specifically binds to a **SRPK** polypeptide comprising any one of 7 fully defined sequences of 338-1017 amino acids given in the specification, where p53 function is restored; (2) modulating p53 pathway in a mammalian cell comprises contacting the cell with an agent that specifically binds to a **SRPK** polypeptide or nucleic acid; and (3) diagnosing a disease in a patient comprises obtaining a biological sample from the patient, contacting the sample with a probe for **SRPK expression**, comparing the results with a control, and determining whether it indicates a likelihood of a disease.

BIOTECHNOLOGY - Preferred Method: Identifying a candidate p53 pathway-modulating agent, where the assay system comprises cultured cells that **express** the serine/arginine protein-specific kinase (**SRPK**) polypeptide. The cultured cells additionally have defective p53 function. The assay system is selected from the group of an apoptosis assay system, a cell proliferation assay system, an angiogenesis assay system, or a hypoxic induction assay system. The assay system includes: (a) a screening assay comprising a **SRPK** polypeptide and the candidate test agent is a small molecule modulator, where the assay is preferably a kinase assay; (b) a binding assay comprising a **SRPK** polypeptide and the candidate test agent is an antibody; or (c) an **expression** assay comprising a **SRPK** nucleic acid and the candidate test agent is a nucleic acid modulator, which is an antisense oligomer or a phosphothioate morpholino oligomer (PMO). (M1) further

comprises administering the identified candidate p53 pathway-modulating agent to a model system comprising cells defective in p53 function, and detecting a phenotypic change in the model system that indicates that the p53 function is restored. The model system is a mouse model system with defective p53 function and additionally comprises: (a) providing a secondary assay system comprising cultured cells or a non-human animal **expressing SRPK**; (b) contacting the secondary assay system with the test agent, or an agent derived from it under conditions, where but for the presence of the test agent or the agent derived from it, the system provides a reference activity; and (c) detecting an agent-biased activity of the second assay system, where a difference between the agent-biased activity and the reference activity of the second assay system confirms the test agent or agent derived from it as a candidate p53 pathway-modulating agent, and where the second assay detects an agent-biased change in the p53 pathway.The secondary assay system comprises cultured cells or a non-human animal, which mis-**expresses** a p53 pathway gene. Modulating a p53 pathway of a cell, where the candidate modulator is administered to a vertebrate animal pre-determined to have a disease or disorder resulting from a defect in p53 function. The candidate modulator is an antibody or a small molecule. Modulating p53 pathway in a mammalian cell, where the agent is administered to a mammalian animal pre-determined to have a pathology associated with the p53 pathway. The agent is a small molecule modulator, a nucleic acid modulator, or an antibody. Diagnosing a disease in a patient, where the disease is cancer, preferably breast cancer, colon cancer, lung cancer, or ovarian cancer, which has greater than 25% **expression** level.

ACTIVITY - Cytostatic. Test details are described but no results given.

MECHANISM OF ACTION - P53 Agonist; P53 Antagonist.

USE - Invention provides methods for utilizing p53 modifier genes and polypeptides to identify candidate therapeutic agents that can be used in the treatment of disorders associated with defective p53 function. The methods are also useful for modulating p53 pathway in a mammalian cell, or for diagnosing or treating a disease associated with defective p53 function, e.g. cancers such as breast cancer, colon cancer, lung cancer or ovarian cancer. The serine/arginine protein-specific kinase (**SRPK**) polypeptides and nucleic acids are useful for identifying and testing agents that modulate **SRPK** function. The animal models are useful for in vivo assays to test the activity of a candidate p53-modulating agent, or to assess the role of **SRPK** in a p53 pathway process such as apoptosis or cell proliferation.

ADMINISTRATION - Dosage of the antibody is approx. 0.1-10 mg/kg bodyweight.

EXAMPLE - Fluorescently-labeled serine/arginine protein-specific kinase (**SRPK**) peptide/substrate were added to each well of a 96-well microtiter plate, along with a test agent in a test buffer. Changes in fluorescence polarization, determined by using a Fluorolite FPM-2 Fluorescence Polarization Microtiter System, relative to control values indicates the test compound is a candidate modifier of **SRPK** activity.(137 pages)

L15 ANSWER 15 OF 21 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-03137 BIOTECHDS
TITLE: New **SR** protein-specific **kinase** 2 peptides and nucleic acid sequences, useful as models for developing **human** therapeutic targets, in identifying therapeutic proteins, and in identifying agents that modulate kinase activity;
recombinant enzyme protein production and sense and antisense use in gene therapy
AUTHOR: ABU-THREIDEH J; **GONG F**; **KETCHUM K A**; DI FRANCESCO V; **BEASLEY E M**

PATENT ASSIGNEE: ABU-THREIDEH J; GONG F; KETCHUM K A; DI FRANCESCO V; BEASLEY E M
PATENT INFO: US 2002094560 18 Jul 2002
APPLICATION INFO: US 2001-759359 16 Jan 2001
PRIORITY INFO: US 2001-759359 16 Jan 2001; US 2001-759359 16 Jan 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-681805 [73]

AB DERWENT ABSTRACT:

NOVELTY - An isolated **human** kinase peptide, is new.

DETAILED DESCRIPTION - An isolated **human** kinase peptide, comprising or consisting of: (a) a fully defined sequence of 699 amino acids (I) given in the specification; (b) an allelic variant or an ortholog of (I) encoded by a nucleic acid that hybridizes under stringent conditions to the opposite strand of a nucleic acid having a sequence of 3253 (II) or 90541 (III) bp given in the specification; or (c) a fragment of (I) comprising at least 10 contiguous amino acids. INDEPENDENT CLAIMS are also included for the following: (1) an isolated antibody that selectively binds to the peptide; (2) an isolated nucleic acid molecule consisting or comprising: (a) a nucleotide sequence encoding (I); (b) a nucleotide sequence that encodes an allelic variant or ortholog of (I) and that hybridizes under stringent conditions to the opposite strand of (II) or (III); (c) a nucleotide sequence that encodes a fragment of (I) comprising at least 10 contiguous amino acids; (d) a complement of (a)-(c); (3) a gene chip comprising the nucleic acid; (4) a transgenic non-**human** animal comprising the nucleic acid; (5) a nucleic acid vector comprising the nucleic acid; (6) a host cell containing the nucleic acid vector; (7) a method for producing the peptide defined above by introducing a nucleotide sequence encoding an amino acid sequence defined above into a host cell, and culturing the host cell under conditions in which the peptides are expressed from the nucleotide sequence; (8) a method for detecting the presence of a nucleic acid molecule as defined above, in a sample, by contacting the sample with an oligonucleotide that hybridizes to the nucleic acid molecule under stringent conditions, and determining whether the oligonucleotide binds to the nucleic acid molecule in the sample; (9) a method for identifying a modulator of a peptide defined above with an agent, and determining if the agent has modulated the function or activity of the peptide; (10) a method for identifying an agent that binds to a peptide defined above, by contacting the peptide with an agent and assaying the contacted mixture to determine whether a complex is formed with the agent bound to the peptide; (11) a pharmaceutical composition comprising an agent identified by the method of (10), and a pharmaceutical carrier; (12) a method of treating a disease or condition mediated by a **human** kinase protein by administering an agent identified in (10); (13) a method for identifying a modulator of the expression of a peptide defined above, by contacting the cell expressing the peptide with an agent, and determining if the agent has modulated the expression of the peptide; (14) an isolated **human** kinase peptide having an amino acids sequence that shares at least 70% homology with (I); and (15) an isolated nucleic acid molecule encoding a **human** kinase peptide and sharing at least 80% homology with (II) or (III).

BIOTECHNOLOGY - Preparation: The peptides are isolated from cells by standard isolation techniques. Preferred Method: The agent is administered to a host cell comprising an expression vector that expresses the peptide. Preferred Sequence: The **human** kinase peptide preferably shares at least 90% homology with (I). The nucleic acid encoding the **human** kinase peptide preferably shares at least 90% homology with (II) or (III).

USE - The **SR** protein-specific **kinase** 2 peptide and nucleic acid sequences can be used as models for the development of **human** therapeutic targets, aid in the identification of therapeutic proteins, and as targets for the development of **human**

therapeutic agents that modulate kinase activity in cells and tissues that express the kinase. These may further be used as query sequences to perform a search against sequence databases to identify other family members or related sequences. The peptides can also be used to raise antibodies or to elicit another immune response, as markers for tissues in which the corresponding protein is preferentially expressed, to identify the binding partner/ligand to develop a system to identify inhibitors of the binding interaction, and in pharmacogenomic analysis. The nucleic acids are useful as probes or primers, for expressing antigenic portions of the proteins, for constructing vectors, host cells or transgenic animals expressing the nucleic acids and peptide, for monitoring the effectiveness of modulating compounds on the expression or activity of the kinase gene in clinical trials or in treatment regimen, and as antisense constructs to control kinase gene expression.

EXAMPLE - No example given. (56 pages)

L15 ANSWER 16 OF 21 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-16041 BIOTECHDS
TITLE: Identifying agents for treatment or prevention of cytomegalovirus infection, comprises contacting test compound with cellular kinase and detecting change in cellular kinase activity;
enzyme inhibition, differential display method and DNA array for disease therapy and drug screening
AUTHOR: SCHUBART D; HABENBERGER P; STEIN-GERLACH M; BEVEC D
PATENT ASSIGNEE: AXXIMA PHARM AG
PATENT INFO: EP 1201765 2 May 2002
APPLICATION INFO: EP 2000-124604 16 Oct 2000
PRIORITY INFO: US 2000-240750 16 Oct 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-373930 [41]
AB DERWENT ABSTRACT:

NOVELTY - Identifying compounds (A) for treating and/or preventing cytomegalovirus (CMV) infection and/or related diseases comprising contacting a test compound with at least one of the cellular kinases RICK, RIP, Nck-Interacting kinase, MKK3 and **SRPK**-2 (undefined) and detecting any change in kinase activity, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) detecting CMV infection and/or related diseases by detecting activity of any of the specified kinases in a patient sample, cells or cell lysates; (2) mono- or poly-**clonal** antibodies (Ab) that bind to any of the specified kinases; (3) preventing and/or treating CMV infection or related diseases, or for regulating production of CMV in an individual or cells, by administering an inhibitor or activator of any of the specified kinases; (4) oligonucleotides (ON) that bind to RNA or DNA encoding any of the specified kinases; (5) regulating **expression** of any of the specified kinases by administering to an individual, or cells, an inhibitor or activator of transcription of the relevant DNA or translation of the relevant RNA; (6) solid support for detecting CMV infection in an individual or cell comprising at least one immobilized ON able to detect activity of any of the specified kinases; and (7) solid support for screening (A) comprising one or more immobilized ON that encode any of the specified kinases or these kinases themselves.

BIOTECHNOLOGY - Preparation: Differential display methods, using a microarray of more than 1100 signal-transduction cDNAs, was used to compare RNA **expression** profiles in CMV infected and non-infected foreskin fibroblasts, to identify the specified kinases as being upregulated in infected cells. The significance of these kinases was confirmed from the much reduced replication of CMV in cells that **express** a mutant form of RICK or RIP. Preferred Method: In the array used to determine mRNA **expression**, preferred immobilized

cDNA oligonucleotides contain 914-2501; 1421-2617; 231-3077; 341-2030 or 1238-2790 base pairs, respectively, regions of RICK, RIP, NIK, MKK3 or **SRPK**-2. Alternatively, determination is at the protein level, e.g. by Western blotting or radioimmunoassay.

ACTIVITY - Virucide. RICK was transiently overexpressed, as a fusion with a hemagglutinin (HA) tag, in human embryonic kidney 293 cells, then immunoprecipitated (anti-HA antibody and protein A-Sepharose). The beads were washed, then tested for kinase activity by incubation in a mixture containing gamma(33P)-adenosine triphosphate and various concentrations of 8-methyl-6-phenyl-2-(pyridin-4-ylamino)-8H-pyrido(2,3-d)pyrimidin-7-one (Aa). After 30 minutes at 30 degrees C, reaction was stopped and phosphorylation determined by electrophoresis and autoradiography. (Aa) has an inhibitory concentration (IC)50 for inhibition of RICK of 500 nM and for inhibition of CMV of 1.4 micro M.

MECHANISM OF ACTION - Modulation of cellular kinases that are specifically upregulated during CMV infection.

USE - (A) are used to treat and/or prevent CMV infections and related diseases. Oligonucleotides that can detect the specified kinases can also be used for diagnosis of infection.

ADMINISTRATION - (A) are administered by inhalation or injection, orally etc. No doses are suggested. (49 pages)

L15 ANSWER 17 OF 21 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:330742 SCISEARCH
THE GENUINE ARTICLE: 188VF
TITLE: Localization of serine kinases, SRPK1 (SFRSK1) and SRPK2 (SFRSK2), specific for the SR family of splicing factors in mouse and human chromosomes
AUTHOR: Wang H Y; Arden K C; Bermingham J R; Viars C S; Lin W; Boyer A D; Fu X D (Reprint)
CORPORATE SOURCE: UNIV CALIF SAN DIEGO, DIV CELLULAR & MOL MED, 9500 GILMAN DR, LA JOLLA, CA 92093 (Reprint); UNIV CALIF SAN DIEGO, DIV CELLULAR & MOL MED, LA JOLLA, CA 92093; UNIV CALIF SAN DIEGO, LUDWIG INST CANC RES, LA JOLLA, CA 92093; UNIV CALIF SAN DIEGO, HOWARD HUGHES MED INST, DEPT MED, LA JOLLA, CA 92093; UNIV CALIF SAN DIEGO, PROGRAM MOL PATHOL, DEPT PATHOL, LA JOLLA, CA 92093; TONGJI MED UNIV, DEPT PEDIAT, WUHAN 430030, HUBEI, PEOPLES R CHINA; XIE HE HOSP, WUHAN 430030, HUBEI, PEOPLES R CHINA
COUNTRY OF AUTHOR: USA; PEOPLES R CHINA
SOURCE: GENOMICS, (15 APR 1999) Vol. 57, No. 2, pp. 310-315. Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495. ISSN: 0888-7543.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 28

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The serine- and arginine-rich (SR) splicing factors play an important role in both constitutive and alternative pre-mRNA splicing, and the functions of these splicing factors are regulated by phosphorylation. We have previously characterized SRPK1 (SFRSK1) and SRPK2 (SFRSK2), which are highly specific protein kinases for the SR family of splicing factors. Here we report the chromosomal localization of the mouse and human genes for both kinases. SRPK1 probes detected two loci that were mapped to mouse Chromosomes 17 and X using The Jackson Laboratory interspecific backcross DNA panel, and SRPK2 probes identified a single locus on mouse Chromosome 5. Using a somatic cell hybrid mapping panel and by fluorescence in situ hybridization, SRPK1 and SRPK2 were respectively mapped to human chromosomes 6p21.2-p21.3 (a region of conserved synteny to mouse Chromosome 17) and 7q22-q31.1 (a region of conserved synteny to mouse

Chromosome 5). In addition, we also found multiple **SRPK**-related sequences on other human chromosomes, one of which appears to correspond to a SRPK2 pseudogene on human chromosome 8. (C) 1999 Academic Press.

L15 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:224990 HCAPLUS
TITLE: Construction of a cDNA **expression** library of Physarum polycephalum at G2 phase
AUTHOR(S): Zhang, Jian-hua; Liu, Shi-de; Xing, Miao
CORPORATE SOURCE: Shenzhen Key Laboratory of Microbial Gene Engineering, College of Life Science, Shenzhen University, Shenzhen, 518060, Peop. Rep. China
SOURCE: Shenzhen Daxue Xuebao, Ligongban (2005), 22(1), 50-56
CODEN: SDXLEX; ISSN: 1000-2618
PUBLISHER: Shenzhen Daxue Xuebao, Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB In order to isolate the genes of SC35-like proteins and **SRPK** -like proteins of Physarum polycephalum, a cDNA **expression** library of P. polycephalum at G2 phase was constructed. The titer of the primary cDNA library is 1.22 + 106 pfu/mL and of the amplified library is 1.12 + 1011 pfu/mL (plaque-forming units, pfu). Almost all of the phages in the cDNA library were reconstituted. The size of the inserts ranges from 0.5 kb to 2.5 kb. All of the above mentioned have answered for the general requirements of a cDNA **expression** library.

L15 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:399415 HCAPLUS
DOCUMENT NUMBER: 139:162417
TITLE: Mediation of the localization of splicing factors in vitro by serine/arginine protein kinase
AUTHOR(S): Lin, Wen; Liu, Zhao; Wang, Huanyou; Fu, Xiangdong
CORPORATE SOURCE: Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, Peop. Rep. China
SOURCE: Zhongguo Zuzhi Huaxue Yu Xibao Huaxue Zazhi (2002), 11(2), 199-201, 240
CODEN: ZZXZFZ; ISSN: 1004-1850
PUBLISHER: Zhongguo Zuzhi Huaxue Yu Xibao Huaxue Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Provide evidence that the serine/arginine protein kinase (**SRPK**) family members mediate the localization of splicing factors in the nucleus. The localizations of both SRPK1 and SRPK2 were determined by peptide tagging or fusing to green fluorescent protein (GFP), and the effect of the **expression** of these kinases on the localization of endogenous splicing factors was examined The results showed that both of these kinases were found in the nucleus and in the cytoplasm, and it was likely that the endogenous kinases were present in both cellular compartments. The splicing factors were concentrated in nuclear speckles in untransfected cells, but diffusely localized in cells **expressing** SRPK1 and SRPK2. The results indicated that **SRPK** family of kinases appears to specifically mediate the redistribution of splicing factors in nucleus.

L15 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:540194 HCAPLUS
DOCUMENT NUMBER: 137:105745
TITLE: Identification, cloning, genomic and cDNA sequences and therapeutic use of a **human** protein kinase SRPK2 alternative splice form
INVENTOR(S): Abu-Threideh, Jane; Gong, Fangcheng; **Ketchum,**

Karen A.; Di Francesco, Valentina; Beasley, Ellen M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 56 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002094560	A1	20020718	US 2001-759359	20010116
US 6492153	B2	20021210		
CA 2435200	AA	20020725	CA 2002-2435200	20020109
WO 2002057458	A2	20020725	WO 2002-US37	20020109
WO 2002057458	A3	20030918		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1360302	A2	20031112	EP 2002-708938	20020109
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003175927	A1	20030918	US 2002-207973	20020731
US 6753175	B2	20040622		
US 2004157297	A1	20040812	US 2004-799676	20040315

PRIORITY APPLN. INFO.:

US 2001-759359	A	20010116
WO 2002-US37	W	20020109
US 2002-207973	A3	20020731

AB The cDNA and genomic sequences and the encoded amino acid sequences of a novel alternative splice form of **SR** protein-specific **kinase** 2 (SRPK2) from **human** are disclosed. Chromosomal mapping of the SRPK2 isoform gene, tissue-specific expression profiles and structural motifs of the polypeptide are provided. The present invention specifically provides isolated peptide and nucleic acid mols., methods of identifying orthologs and paralogs of the kinase peptides, and methods of identifying modulators of the kinase peptides.

L15 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:683191 HCAPLUS
DOCUMENT NUMBER: 136:397779
TITLE: Sequencing and analysis of serine/arginine protein-specific kinase
AUTHOR(S): Lin, Wen; Hu, Wensheng; Wang, Huanyou; Fu, Xiangdong
CORPORATE SOURCE: Department of Pediatrics, Xiehe Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, Peop. Rep. China
SOURCE: Tongji Yike Daxue Xuebao (2001), 30(3), 245-247
CODEN: TYDXEP; ISSN: 0258-2090
PUBLISHER: Tongji Yike Daxue
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Serine/arginine protein-specific kinase (SRPK2) was **cloned** to prepare probes. All 8 SRPK1-related EST cDNA **clones** were sequenced by using Erase-a-Base. DNA probes derived from one **clone** were used to screen a human fetal brain cDNA library in the

Lamda ZAP II vector. A longest **clone**, 3.744 kb, was sequenced in both strands. The results showed that SRPK2 displayed 77% identity and 90% similarity to SRPK1 over their entire kinase domains. In addition, SRPK2 contained a stretch of proline-rich sequence at the N-terminus. The results showed that SRPK2 might be a new **SRPK** family member with its sequence similar to SRPK1, suggesting both SRPK2 and SRPK1 might have similar enzymic activity and substrate specificity. The N-terminal proline-rich motif might function as a targeting signal to interact with substrates and (or) regulators.

=> d his

(FILE 'HOME' ENTERED AT 08:53:58 ON 03 JUN 2005)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 08:54:24 ON 03 JUN 2005

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L1      1322846 S KINASE?
L2          551 S SR (5W)L1
L3          166 S HUMAN AND L2
L4           62 DUP REM L3 (104 DUPLICATES REMOVED)
L5          109 S "SRPK"
L6      7101940 S CLON? OR EXPRESS? OR RECOMBINANT
L7           54 S L5 AND L6
L8           19 DUP REM L7 (35 DUPLICATES REMOVED)
                E ABU-THREIDEH J/AU
                E ABU  J T/AU
                E GONG F/AU
L9          238 S E3
                E KETCHUM K A/AU
L10         480 S E3-E7
                E DIFRANCESCO V/AU
L11         100 S E3
                E BEASLEY E M/AU
L12         327 S E3
L13         993 S L8 OR L9 OR L10 OR L11 OR L12
L14         227 S L3 OR L5
L15          21 S L13 AND L14
```

	L #	Hits	Search Text
1	L1	59920	kinase$2
2	L2	486063	human
3	L3	19454	l1 same l2
4	L4	60980	serine or threonine
5	L5	2346	l3 same l4
6	L6	737420	clon$3 or express$3 or recombinant
7	L7	1220	l5 same l6
8	L8	27	"SRPK"
9	L9	26	l1 same l8
10	L10	35201	splice
11	L11	68	l7 same l10
12	L12	7824	GONG BU-THREIDEH-JANE KETCHUM BEASLEY
13	L13	12	l8 and l12

	Issue Date	Pages	Document ID	Title
1	20041028	63	US 20040213794 A1	Mst1 modulation of apoptosis in cardiac tissue and modultors of Mst1 for treatment and prevention of cardiac disease
2	20041007	190	US 20040197792 A1	Novel Kinases
3	20040812	102	US 20040157297 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
4	20040805	53	US 20040152123 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
5	20040610	22	US 20040110177 A1	Method for identifying functional nucleic acids
6	20040311	152	US 20040048310 A1	Novel human protein kinases and protein kinase-like enzymes
7	20040115	73	US 20040010136 A1	Composition for the detection of signaling pathway gene expression
8	20040115	314	US 20040009549 A1	Method for detecting remote homologues and novel kinases identified with the method
9	20031204	73	US 20030224378 A1	Novel human protein kinases and protein kinase-like enzymes
10	20031127	103	US 20030220224 A1	Novel polynucleotides encoding the human citron kinase polypeptide, BMSNKC_0020/0021

	Issue Date	Pages	Document ID	Title
11	20031120	248	US 20030215840 A1	Methods and compositions for treating cardiovascular disease using 1682, 6169, 6193, 7771, 14395, 29002, 33216, 43726, 69292, 26156, 32427, 2402, 7747, 1720, 9151, 60491, 1371, 7077, 33207, 1419, 18036, 16105, 38650, 14245, 58848, 1870, 25856, 32394, 3484, 345, 9252, 9135, 10532, 18610, 8165, 2448, 2445, 64624, 84237, 8912, 2868, 283, 2554, 9464, 17799, 26686, 43848, 32135, 12208, 2914, 51130, 19489, 21833, 2917, 59590, 15992, 2094, 2252, 3474, 9792, 15400, 1452 or 6585 molecules
12	20031113	86	US 20030211989 A1	Novel human protein kinases and protein kinase-like enzymes
13	20030918	102	US 20030175927 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
14	20030717	53	US 20030134319 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
15	20030501	37	US 20030082519 A1	Cellular kinases involved in Cytomegalovirus infection and their inhibition
16	20020829	53	US 20020119548 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof

	Issue Date	Pages	Document ID	Title
17	20020718	56	US 20020094560 A1	ISOLATED HUMAN KINASE PROTEINS, NUCLEIC ACID MOLECULES ENCODING HUMAN KINASE PROTEINS, AND USES THEREOF
18	20020620	52	US 20020076783 A1	Plants and plants cells expressing histidine tagged intimin
19	20050201	34	US 6849409 B2	Cellular kinases involved in Cytomegalovirus infection and their inhibition
20	20040622	98	US 6753175 B2	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
21	20040511	50	US 6733978 B2	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
22	20031007	50	US 6630337 B2	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
23	20021231	65	US 6500938 B1	Composition for the detection of signaling pathway gene expression
24	20021210	95	US 6492153 B2	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
25	20020924	50	US 6455291 B1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
26	19960924	42	US 5559019 A	Protein serine kinase, SRPK1

	Issue Date	Pages	Document ID	Title
1	20050407	107	US 20050074793 A1	Metastatic colorectal cancer signatures
2	20050217	95	US 20050037430 A1	Methods and uses for protein breakdown products
3	20041209	34	US 20040248286 A1	Nucleic acid molecules that are differentially regulated in a bipolar disorder and uses thereof
4	20041104	138	US 20040219521 A1	Novel nucleic acids and polypeptides
5	20040909	69	US 20040175743 A1	Methods for monitoring drug activities in vivo
6	20040722	293	US 20040142335 A1	Method for determining skin stress or skin ageing in vitro
7	20040527	85	US 20040101885 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
8	20040506	179	US 20040086913 A1	Human genes and gene expression products XVI
9	20040422	32	US 20040077020 A1	Diagnostic microarray for inflammatory bowel disease, crohn's disease and ulcerative colitis
10	20040415	337	US 20040072160 A1	Molecular toxicology modeling
11	20040325	82	US 20040058325 A1	Gene expression in biological conditions
12	20040318	209	US 20040053317 A1	Gene segregation and biological sample classification methods
13	20040318	243	US 20040053248 A1	Novel nucleic acids and polypeptides

	Issue Date	Pages	Document ID	Title
14	20040318	108	US 20040052777 A1	Kringle polypeptides and methods for using them to inhibit angiogenesis
15	20040311	62	US 20040048305 A1	14171 Protein kinase, a novel human protein kinase and uses thereof
16	20040311	267	US 20040048249 A1	Novel nucleic acids and secreted polypeptides
17	20040226	259	US 20040038207 A1	Gene expression in bladder tumors
18	20040219	88	US 20040033502 A1	Gene expression profiles in esophageal tissue
19	20040219	324	US 20040033495 A1	Methods of diagnosis of angiogenesis, compositions and methods of screening for angiogenesis modulators
20	20040212	570	US 20040029114 A1	Methods of diagnosis of breast cancer, compositions and methods of screening for modulators of breast cancer
21	20040115	73	US 20040010136 A1	Composition for the detection of signaling pathway gene expression
22	20040115	484	US 20040009479 A1	Methods and compositions for diagnosing or monitoring auto immune and chronic inflammatory diseases
23	20040108	52	US 20040005612 A1	Endometrial genes in endometrial disorders
24	20040108	345	US 20040005563 A1	Methods of diagnosis of ovarian cancer, compositions and methods of screening for modulators of ovarian cancer

	Issue Date	Pages	Document ID	Title
25	20040101	106	US 20040002067 A1	Breast cancer progression signatures
26	20031225	222	US 20030235820 A1	Novel methods of diagnosis of metastatic colorectal cancer, compositions and methods of screening for modulators of metastatic colorectal cancer
27	20031218	150	US 20030232421 A1	Protein-protein interactions in adipocyte cells (3)
28	20031204	23	US 20030224440 A1	Human VNO cDNA libraries
29	20031106	128	US 20030207311 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
30	20030918	74	US 20030176651 A1	Multiprotein-complex comprising a nmda receptor and uses thereof
31	20030918	23	US 20030176375 A1	Method of treating anemia
32	20030626	80	US 20030119720 A1	Oligopeptide treatment of anthrax
33	20030619	77	US 20030113733 A1	Gene regulator
34	20030605	54	US 20030104393 A1	Blood assessment of injury
35	20030508	88	US 20030086934 A1	Basal cell markers in breast cancer and uses thereof
36	20030327	54	US 20030059918 A1	Regulation of human serine/threonine protein kinase
37	20030313	95	US 20030049828 A1	MN gene and protein

	Issue Date	Pages	Document ID	Title
38	20030213	112	US 20030030637 A1	Method and system for data analysis
39	20030116	112	US 20030014420 A1	Method and system for data analysis
40	20021226	179	US 20020198362 A1	Compositions and methods for the detection, diagnosis and therapy of hematological malignancies
41	20021219	195	US 20020192678 A1	Genes expressed in senescence
42	20021212	113	US 20020188424 A1	Method and system for data analysis
43	20021114	17	US 20020168670 A1	Identification of disease predictive nucleic acids
44	20021024	22	US 20020155444 A1	Human VNO cDNA libraries
45	20021010	21	US 20020147320 A1	Novel human kinase proteins and polynucleotides encoding the same
46	20020919	89	US 20020132325 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
47	20020808	21	US 20020106771 A1	Nucleic acids encoding CLK protein kinases
48	20011122	16	US 20010044104 A1	Genes defferentially expressed in secretory versus proliferative endometrium
49	20050531	20	US 6900045 B2	Human kinase proteins and polynucleotides encoding the same
50	20050426	15	US 6884578 B2	Genes differentially expressed in secretory versus proliferative endometrium

	Issue Date	Pages	Document ID	Title
51	20050201	37	US 6849420 B2	Method for determining modulation of p110.delta. activity
52	20050111	10	US 6841348 B1	Methods for identifying and using maintenance genes
53	20041005	40	US 6800436 B1	Diagnostic method, diagnostic reagent and therapeutic preparation for diseases caused by variation in LKB1 gene
54	20040420	59	US 6723837 B1	Nucleic acid molecule and encoded protein associated with sterol synthesis and metabolism
55	20040217	29	US 6693226 B1	Transgenic mice expressing human p25
56	20031216	81	US 6664085 B2	Isolated human calcium/calmodulin (CaMk) dependent kinase proteins
57	20030701	95	US 6586185 B2	Use of polypeptides or nucleic acids for the diagnosis or treatment of skin disorders and wound healing and for the identification of pharmacologically active substances
58	20021231	65	US 6500938 B1	Composition for the detection of signaling pathway gene expression
59	20021119	35	US 6482623 B1	Lipid kinase
60	20020917	17	US 6451524 B1	Identification of disease predictive nucleic acids
61	20020514	85	US 6387677 B1	Nucleic acid molecules encoding human calcium/calmodulin (CaMK) dependent kinase proteins
62	20020101	227	US 6335170 B1	Gene expression in bladder tumors

	Issue Date	Pages	Document ID	Title
63	20011218	87	US 6331396 B1	Arrays for identifying agents which mimic or inhibit the activity of interferons
64	20011127	21	US 6323318 B1	Human protein kinases hYAK3-2
65	20011002	95	US 6297051 B1	MN gene and protein
66	20010529	637	US 6239264 B1	Genomic DNA sequences of ashbya gossypii and uses thereof
67	20001226	19	US 6165766 A	Human protein kinases hYAK3
68	19991012	20	US 5965420 A	Human protein kinases hYAK3

	Issue Date	Pages	Document ID	Title
1	20040812	102	US 20040157297 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
2	20040805	53	US 20040152123 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
3	20030918	102	US 20030175927 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
4	20030717	53	US 20030134319 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
5	20020829	53	US 20020119548 A1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
6	20020718	56	US 20020094560 A1	ISOLATED HUMAN KINASE PROTEINS, NUCLEIC ACID MOLECULES ENCODING HUMAN KINASE PROTEINS, AND USES THEREOF
7	20020620	52	US 20020076783 A1	Plants and plants cells expressing histidine tagged intimin
8	20040622	98	US 6753175 B2	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
9	20040511	50	US 6733978 B2	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof

10	20031007	50	US 6630337 B2	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof

	Issue Date	Pages	Document ID	Title
11	20021210	95	US 6492153 B2	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof
12	20020924	50	US 6455291 B1	Isolated human kinase proteins, nucleic acid molecules encoding human kinase proteins, and uses thereof